Effect of Monthly High-Dose Vitamin D Supplementation on Risk of Cancer: the Vitamin D Assessment Study (a Randomized Controlled Trial)

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Key points

Question: Does monthly high-dose vitamin D supplementation prevent cancer?

Findings: In a randomized clinical trial that included 5108 participants from the community, the cumulative incidence of cancer over a median follow-up period of 3.3 years was 6.5% in participants given 100,000 IU monthly doses of vitamin D3 and 6.4% in those given placebo.

Meaning: Monthly high-dose vitamin D supplementation did not prevent cancer and should not be used for this purpose.
Abstract

Importance: Previous randomized controlled trials have provided inconsistent results on the effect of vitamin D supplementation on cancer incidence.

Objective: To determine if monthly high-dose vitamin D supplementation, without calcium, reduces cancer incidence and cancer mortality in the general population.

Design: Randomized, double-blind, placebo-controlled trial, participants recruited from April 2011 to November 2012, follow-up until December 2015.

Setting: Recruited mostly from family practices in Auckland, New Zealand.

Participants: Community-resident adults, aged 50-84 years. Out of 47,905 adults invited from family practices, and 163 from community groups, 5,110 participants were randomized to vitamin D3 (n=2,558) or placebo (n=2,552). Two participants withdrew consent, and all others (n=5,108) were included in the primary analysis.

Intervention: Oral vitamin D3, initial bolus dose of 200,000 IU, followed one month later by monthly doses of 100,000 IU, or placebo, for median of 3.3 years (range: 2.5–4.2 years).

Main Outcomes and Measures: The post-hoc primary outcome was all primary neoplasms (invasive and in-situ), aside from non-melanoma skin cancers, diagnosed from randomization to stopping the study medication (31 July 2015). Secondary outcomes were all neoplasms: from randomization to 31 December 2015; from >12 months after randomization to both stopping the study medication and also to 31 December 2015; and fatal neoplasms from randomization to 31 December 2015.

Results: Mean (SD) age was 65.9 (8.3) years, 58% were male, and 83% were white, with the remainder being Polynesian or South Asian. Mean (SD) baseline deseasonalized 25(OH)D
concentration was 26.5 (9.0) ng/mL. In a random sample of 438 participants, mean follow-up 25(OH)D was consistently >20 ng/mL higher in the vitamin D supplemented than placebo group. 

The primary cancer outcome comprised 328 total cancer cases (259 invasive, 69 in situ); and occurred in 6.5% of the vitamin D group and 6.4% of the placebo group, giving an adjusted hazard ratio of 1.01 (95%CI, 0.81–1.25). Similar results were seen for all secondary outcomes, including cancer mortality.

**Conclusions and Relevance:** Monthly high-dose vitamin D supplementation for up to 4 years, without calcium, does not prevent cancer. Further study is required on the effect of daily or weekly dosing for longer duration.

**Trial Registration:** Australian New Zealand Clinical Trials Registry, Identifier ACTRN12611000402943, (https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=336777)
The hypothesis that vitamin D may protect against cancer arose from ecological studies,
published since the 1980s, that reported inverse associations between sun exposure, the major
source of vitamin D, and incidence of several types of cancer.\textsuperscript{1-4} Subsequent meta-analyses of
cohort studies have provided further evidence, with low baseline 25-hydroxyvitamin D
(25(OH)D) concentrations predicting increased cancer risk during follow-up, particularly of
colorectal cancer.\textsuperscript{5-7} In contrast, the recent evidence from Mendelian randomization studies is
inconsistent, with genetically low 25(OH)D concentrations associated with increased risk of
cancer mortality and ovarian cancer in two studies,\textsuperscript{8,9} but not with several types of cancer in a
third.\textsuperscript{10}

Randomized controlled trials (RCT) of vitamin D supplementation have also provided
inconsistent results. The Women’s Health Initiative did not show a protective effect of daily
vitamin D and calcium supplementation against incidence of colorectal, breast and all invasive
cancer, which could have been due to the low vitamin D dose (400 IU/day).\textsuperscript{11-13} In contrast, two
subsequent trials by one research group, which gave a higher vitamin D dose (2000 IU/day)
with calcium, reported a reduced incidence of all types of cancer in the treatment arm.\textsuperscript{14,15} A
consistent finding in both studies was a ~1-year lag from randomization for the vitamin D
benefit to appear on survival curves, although this analysis was not pre-specified.

Given the limited trial evidence on vitamin D supplementation and cancer, we carried
out a post-hoc analysis of a large community-based RCT to determine if vitamin D
supplementation prevents cancer, in a trial where the original primary aim was to assess the
effect of vitamin D supplementation on cardiovascular disease incidence.\textsuperscript{16} We also included
cancer mortality as a secondary outcome, given evidence from a recent meta-analysis suggesting that vitamin D supplements reduce cancer mortality, but not cancer incidence.
Methods

Study Design

The Vitamin D Assessment (ViDA) study is a randomized, double-blind, placebo-controlled trial carried out in Auckland, New Zealand, during 2011-2015. Full details of the study methods have been published. Inclusion criteria were: age 50–84 years; ability to give informed consent; resident in Auckland at recruitment; and anticipated residence in New Zealand for the 4-year study period. Exclusion criteria were: current use of vitamin D supplements, including cod-liver oil (>600 IU/day if aged 50–70 years; >800 IU/day if aged 71–84 years); diagnosis of psychiatric disorders that would limit ability to comply with study protocol; history of hypercalcemia, nephrolithiasis, sarcoidosis, parathyroid disease or gastric bypass surgery; enrolment in another study that could affect participation; or baseline serum-corrected calcium >10.0 mg/dL. The Multi-region Ethics Committee (MEC/09/08/082) approved the study, which was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12611000402943).

Participant Recruitment and Baseline Assessment

Participants were recruited mainly from 55 family practices in Auckland; 94% of New Zealand population is registered with family practices. Starting March 2011, a personalized letter was mailed to the homes of potential participants (n=47,905) inviting them to participate; Out of 8,688 who replied, 5,107 were interested and eligible for baseline assessments. An additional 163 potential participants from ethnic minority community groups were screened,
and 143 were eligible. Altogether, 5,250 had a baseline assessment from 5 April 2011 to 6 November 2012 (Figure 1).

The baseline assessment included collecting written informed consent, followed by questions on: socio-demographic status; lifestyle (tobacco smoking, alcohol drinking over the last 12 months, and usual leisure-time physical activity and sun exposure over the last three months); intake of vitamin D or calcium supplements; and past medical history told by a doctor (including cancer and age of cancer diagnosis). We measured height (±0.1 cm) and weight (±0.1 kg) in light clothing without shoes. A non-fasting blood sample was collected to screen for hypercalcemia, with the remaining serum aliquoted and stored at -80°C for later 25(OH)D measurement.

**Randomization**

After the baseline assessment, participants were mailed a ‘run-in’ questionnaire with a blinded placebo capsule, and were included if they returned the questionnaire within 4 weeks, confirmed in the questionnaire they took the capsule, and did not have hypercalcemia (corrected calcium ≤10.0 mg/dL). A total of 5,110 participants (4,972 from practices, 138 from community) were randomized from 03 June 2011 to 23 January 2013 into one of the two treatment groups, within random blocks of 8, 10 or 12, within ethnic group and 5-year age strata. Treatment was allocated using computer generation by the study biostatistician; all other staff and participants were blinded.
Intervention

Vitamin D₃ (2.5 mg or 100,000 IU) or placebo softgel oral capsules, sourced from Tishcon Corporation (Westbury, NY), were mailed to participants’ homes, with a 1-page questionnaire (and reply-paid envelope) to record self-reported adherence; the return of which was used to monitor retention. Two capsules were sent in the first mail-out post-randomization (i.e., 200,000 IU bolus, or placebo), followed one month later (and thereafter monthly) with 100,000 IU vitamin D₃ or placebo capsules. A monthly 100,000 IU vitamin D dose was chosen as pharmacokinetic research showed this dose maintained serum 25(OH)D levels >35 ng/mL for a month post-ingestion. The aim was to raise serum 25(OH)D throughout the year to 32-40 ng/mL, which observational studies then suggested was optimal for health. Capsules continued to be mailed monthly until June 2013. For cost reasons, from July 2013 onward, four capsules were mailed every four months, with monthly email/letter reminders to participants to take their monthly capsule. Questionnaires were mailed monthly until November 2013, and then from March 2014 onward were sent 4-monthly with the four capsules. Participants stopped their assigned study medication on 31 July 2015.

Serum Calcium and 25-Hydroxyvitamin D

Serum-corrected calcium was measured at baseline on an Advia 2400 analyser (Siemens Healthcare Diagnostics, Eschborn, Germany). Serum 25(OH)D, combining D₂ and D₃, was measured in baseline aliquots stored frozen at −80°C (−112°F) by liquid chromatography–tandem mass spectrometry (ABSciex API 4000, Framingham, MA) with 12.7% inter-assay coefficient of variation in a local laboratory participating in the Vitamin D External Quality
Assessment Scheme program (www.degas.org). In a 10% random sample, 438 (85% of 515 invited) participants agreed to return at 6, 12, 24 and 36 months for collection of further blood samples to measure corrected calcium (on fresh blood) and 25(OH)D (on stored blood, measured in the same batch for each participant). Season-adjusted (deseasonalized) 25(OH)D values were calculated for each participant from their individual baseline 25(OH)D concentration and blood collection date, using a sinusoidal model with parameters derived from baseline values for all participants. Vitamin D deficiency was defined as a deseasonalized 25(OH)D <20 ng/mL.

Cancer Outcomes

The New Zealand Ministry of Health maintains registries of all primary neoplasms (invasive and in-situ) diagnosed (from pathology reports including cancer site and morphology) in New Zealand, excluding non-melanoma skin cancers, and of all deaths. The accuracy of the cancer registry is similar to clinical audits of cancer registries in the US and Europe.

All New Zealand residents are assigned a unique Ministry of Health National Health Index (NHI) number. These were collected from all study participants, who gave their consent for the study researchers to access their Ministry of Health data. The NHI numbers were used to link individuals with cancer registration data and deaths. Information collected about cancer history at the baseline assessment was used to help distinguish between prevalent and incident cases in the Cancer Registry data.
The aim of our analysis was to replicate (as much as possible) the outcome definitions and statistical analysis methods used by Lappe and colleagues.\textsuperscript{15} Cancer cases were defined as ICD-10 codes C00-D09, or cancer deaths.

The primary outcome was time to first cancer reported for all neoplasms (defined above), from randomization to stopping the study medication (31 July 2015). The primary outcome was examined in the following pre-specified groups: overall (all participants); by sex and by baseline desecanlized 25(OH)D level (<20 ng/mL, ≥ 20 ng/mL).

The secondary outcomes were all neoplasms (defined above): reported from >12 months post-randomization to stopping the study medication (31 July 2015), from randomization to 31 December 2015, from one year post-randomization to 31 December 2015; and cancer deaths post-randomization to 31 December 2015. Each secondary outcome was examined in the pre-specified groups described above for the primary outcome. The follow-up period for some secondary outcomes continued for 5 months after stopping supplementation (to 31 December 2015), as serum 25(OH)D remains higher in vitamin D-supplemented people than those on placebo for up to a year after stopping supplementation.\textsuperscript{31}

The study protocol specified identifying new cancer cases, to later combine data for common cancers with cancer data from other vitamin D supplementation trials, but not as an outcome for the ViDA study. As this report is a post-hoc analysis of data collected for other outcomes, we developed the statistical analysis plan for the cancer outcomes (Online Supplement), and registered cancer as a secondary outcome with the trial website on 10 October 2017, before receiving the Ministry of Health cancer data on 08 November 2017.
**Statistical Analysis**

Analysis of the cancer outcomes was conducted on an intention-to-treat basis, using NHI numbers to identify cancer registrations and deaths, regardless of whether participants continued to participate actively in the study by returning home questionnaires. Cox regression proportional hazards models, with robust sandwich variance estimates were used to compare time to first cancer in the two treatment groups. Non-cancer deaths were censored. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC), and p-value <0.05 (two-sided) was considered significant. Weighted Schoenfeld residuals were used to check the proportional hazards assumption which was not violated for any variable in the model – treatment, age, sex and ethnicity (all p>0.05). Based on an overall cumulative incidence of 6.4% (328 cancer cases for primary outcome), the study had 85% power to detect a risk ratio of 0.70 with 2-sided 95% confidence interval (www.openepi.com/Power/PowerRCT.htm).
RESULTS

Recruitment and Baseline Characteristics

From 8,851 participants assessed for eligibility, 5,250 had baseline assessments, and 5,110 were randomized. We later excluded two individuals who withdrew consent post-randomization for their data to be retained by the researchers, so 5,108 were included in the analysis of the primary outcome (Figure 1). Overall, 58% of participants were male, 83% were of “other” ethnicity (96% of whom had European ancestry). At baseline: mean (SD) age was 65.9 (8.3) years; only 6% currently smoked tobacco while 43% were ex-smokers; 24% reported being told by a doctor previously of having had cancer; mean (SD) observed 25(OH)D was 25.3 (9.5) ng/mL and deseasonalized was 26.5 (9.0) ng/mL. Baseline characteristics were similar between vitamin D and placebo groups (Table 1).

Follow-up and Adherence

Figure 1 shows the flow diagram of follow-up after randomization. Fifteen deaths occurred within one year post-randomization, a further 108 by the end of the active follow-up period (31 July 2015), and a further 32 by the end of passive follow-up (31 December 2015). This yielded a total of 155 deaths (75 in vitamin D group, 80 in placebo group) for the total follow-up period.

The majority (98%) of participants confirmed by questionnaire, within 2 months post-randomization, that they had started taking the study capsule, and only 21 (1%) of the vitamin D group and 49 (2%) of the placebo group never confirmed this during the active follow-up period from randomization to 31 July 2015 (median 3.3 years; range 2.5 to 4.2 years). During the last five months of active follow-up, 87% of participants were actively involved in the trial,
as indicated by the 4,032 (81%) who returned the final July 2015 questionnaire and a further
283 (6%) who returned the penultimate March 2015 questionnaire.

Adherence to taking the study capsule reported in the home questionnaires was 85% in
the vitamin D group and 83% in the placebo (84% overall, 168,667 capsules reported taken
during 200,936 person-months) up to 31 July 2015. This high adherence was confirmed by the
mean observed 25(OH)D concentrations of the randomly-selected participants who returned to
give blood samples at 6 months, and up to 36 months post-randomization, which ranged from
48 to 54 ng/mL in the vitamin D group, being consistently >20 ng/mL higher than the mean in
the placebo group (Figure e1 in Supplement). Mean (SD) serum calcium levels throughout the
follow-up period in this sub-sample were similar for the vitamin D vs placebo groups, being
respectively, 9.2 (0.4) vs 9.2 (0.4) mg/dL at 6, 12 and 24 months, and 9.6 (0.4) vs 9.6 (0.4) mg/dL
at 36 months. No participants in this sub-sample developed hypercalcemia related to taking the
study capsules.

Cancer Outcomes

There were 375 participants who had a first cancer registration post-randomization (60 of
whom died) and another 29 who died from cancer diagnosed before randomization, giving a
total of 404 participants with a cancer outcome up to 31 December 2015. The types of cancer
are shown in Table 2. The most common cancer was melanoma-in-situ (n=71) and malignant
melanoma (n=55), followed by prostate cancer (n=64), colorectal (n=38), breast (n=36) and
lymphoid and hematopoietic cancers (n=36).
The numbers of participants with the primary and secondary outcomes during follow-up in the vitamin D and placebo groups, along with hazard ratios (HR) adjusted for age, sex, and ethnicity, are shown in Table 3. There was no difference in the percentage of participants with cancer registrations from randomization to 31 July 2015 (primary endpoint) between vitamin D (6.5%) and placebo (6.4%) arms (HR 1.01; 95% CI, 0.81–1.25). Similar results were seen in men (HR 0.96; 95% CI, 0.74–1.25) and women (HR 1.09; 95% CI, 0.75–1.59; $P_{\text{interaction}} = 0.57$), and in participants with 25(OH)D <20 ng/ml (HR 1.01; 95% CI, 0.65–1.58) and ≥20 ng/mL (HR 1.04; 95% CI, 0.81–1.33; $P_{\text{interaction}} = 0.80$). There was no difference between vitamin D and placebo arms in the time to first cancer registration up to 31 July 2015, including from one year post-randomization (Figure 2). Similar results were seen for all secondary outcomes, as well as for non-skin cancers (Table 3). Stratifying the sample by sex and baseline 25(OH)D concentration produced similar results for all secondary outcomes (Table e1 in Supplement).
DISCUSSION

The results of this large RCT show that monthly high-dose vitamin D supplementation did not prevent incident cancer nor reduce cancer mortality in people selected from the community. The cancer incidence results are consistent with findings from previous RCTs of community samples in the US and Britain which reported hazard ratios of 0.98 ($P=0.54$) and 1.09 ($P=0.47$), respectively, and with a recent meta-analysis of vitamin D supplementation trials. However, our results in Table 3 comparing the vitamin D and placebo group do not confirm results of borderline statistical significance from a recent Nebraska study reporting a 35% reduced hazard ratio for follow-up starting from 12 months after randomization ($P=0.047$), nor the 30% reduced hazard ratio for follow-up starting from randomization ($P=0.06$).

Neither do our results confirm a recent meta-analysis of three trials which found that vitamin D supplementation significantly reduced cancer mortality by 12%.

There are several possible explanations for why our trial did not observe a similar reduction in cancer incidence from vitamin D as the recent Nebraska study. First, we gave bolus dosing rather than daily dosing of vitamin D. Recent studies suggest that vitamin D is more able to enter cells than 25(OH)D for conversion to the active metabolite of vitamin D, and in our study vitamin D would only have been present in the blood circulation for several days after each monthly dose because of its short half-life. Thus, the Nebraska study may have produced a stronger continuous vitamin D exposure from their daily dose. Second, we gave vitamin D by itself rather than with calcium. It is possible the effect of both together, acting separately or synergistically, is more effective than vitamin D alone, although a reduction
in cancer incidence was not seen in the Women’s Health Initiative which also gave both 
supplements together. Third, the cancer profile in the ViDA study had a much greater 
proportion of cases with melanoma (33%, Table 2) compared to the Nebraska study (6%), 
although analyses restricted to non-skin cancer produced a similar null result. The similar 
results for men and women in our study (Table 3) suggests that the inclusion of only women in 
the Nebraska study is an unlikely explanation for the difference in the results between our two 
studies.

Other possible reasons for the null result in our study include insufficient participants (25%) 
with vitamin D deficiency, which limited statistical power in that subgroup. However, the lower 
mean baseline observed 25(OH)D concentration in the ViDA study compared with the Nebraska 
study (25.3 versus 32.8 ng/mL) suggests that participants in the former were more likely to be 
vitamin D-deficient. Another possible explanation for the null finding is the relatively short 
follow-up time (median 3.3 years) which may have been too short to detect any effect of 
vitamin D supplementation against cancer.

Our study has important strengths. As our sample was recruited from the community, 
results are likely to be relevant for the general population. Adherence to the study capsule was 
high, as confirmed by the doubling in mean 25(OH)D concentration vitamin D arm of the 
random sub-sample (Supplementary Figure), which was 54.1 ng/mL at 36 months follow-up in 
the vitamin D arm, 9 ng/mL higher than in the Nebraska study. Retention and active 
participation in the study were high: 87% returned the final two questionnaires. We enquired 
extensively at the baseline assessment about cancer history, which allowed us to identify 
cancer cases incident after randomization; and these were systematically identified from the
cancer registry, regardless of whether participants continued to actively participate, allowing us to do intention-to-treat analyses. While our study had 85% power to detect a risk ratio of 0.70, observed in the Nebraska study, our power was much lower for detecting weaker effects against cancer from vitamin D, including the modest 12% reduction in cancer mortality reported in a recent meta-analysis of vitamin D supplementation. In conclusion, we showed that monthly high-dose vitamin D supplementation, for up to 4 years, without calcium, did not prevent cancer. Further research is required on the effects of daily or weekly dosing of vitamin D on cancer risk for longer durations.
Acknowledgement Section

Author Contributions: Dr Scragg had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Scragg, Khaw, Toop, Sluyter, Lawes, Giovannucci, Camargo.

Acquisition of data: Scragg, Waayer, Sluyter, Lawes.

Analysis and interpretation of data: Scragg, Khaw, Toop, Sluyter, Lawes, Waayer, Giovannucci, Camargo.

Drafting of the manuscript: Scragg.

Critical revision of the manuscript for important intellectual content: Scragg, Khaw, Toop, Sluyter, Lawes, Waayer, Giovannucci, Camargo.

Statistical analysis: Scragg.

Obtained funding: Scragg, Lawes, Toop, Khaw, Camargo.

Administrative, technical or material support: Scragg, Sluyter, Lawes, Waayer.

Study supervision: Scragg, Camargo.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form of Disclosure of Potential Conflicts of Interest and none were reported.

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Role of the Sponsors: Neither sponsor was involved in the design or conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.

Additional Contributions: We thank all research staff for carrying out the activities associated with the conduct of the study. We also thank the Data Monitoring Committee of the Health Research Council, and members of the ViDA Scientific Advisory Board. Finally, we thank the study participants and their family doctors for facilitating their participation in the study.
Legend for Figures

Figure 1: Flow diagram for the cancer outcome in the ViDA study.

Figure 2: Proportion (95% CI) of participants developing cancer during follow-up to 31 July 2015, by study group.
REFERENCES


Table 1: Baseline comparison of the vitamin D supplemented and placebo groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Vitamin D (n=2,558)</th>
<th>Placebo (n=2,550)</th>
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<td><strong>Age (years), No. (%)</strong></td>
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<td></td>
</tr>
<tr>
<td>50-59</td>
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<td>567 (22.2)</td>
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<tr>
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<td>1112 (43.5)</td>
<td>1108 (43.5)</td>
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<tr>
<td>70-79</td>
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<td>80-84</td>
<td>159 (6.2)</td>
<td>153 (6.0)</td>
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<td>1457 (57.1)</td>
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<td><strong>Education (highest level), No. (%)</strong></td>
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<td>Primary school</td>
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<td>Tertiary</td>
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<td>1317 (51.6)</td>
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<td>1018 (39.9)</td>
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<td>&lt;1</td>
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<td>&gt;2</td>
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<th>Take supplements, No. (%)</th>
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<td>Vitamin D&lt;sup&gt;b&lt;/sup&gt;</td>
<td>208 (8.1)</td>
<td>200 (7.8)</td>
</tr>
<tr>
<td>Calcium</td>
<td>125 (4.9)</td>
<td>127 (5.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Previous cancer told by a doctor, No. (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes (all cancers)</td>
<td>622 (24.4)</td>
<td>592 (23.3)</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>35 (1.4)</td>
<td>41 (1.6)</td>
</tr>
<tr>
<td>Breast cancer (women)</td>
<td>56 (5.4)</td>
<td>54 (5.0)</td>
</tr>
<tr>
<td>Prostate cancer (men)</td>
<td>94 (6.3)</td>
<td>84 (5.8)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>107 (4.2)</td>
<td>101 (4.0)</td>
</tr>
<tr>
<td>Non-melanoma skin cancer</td>
<td>289 (11.4)</td>
<td>295 (11.6)</td>
</tr>
<tr>
<td>Other</td>
<td>41 (1.6)</td>
<td>17 (0.7)</td>
</tr>
</tbody>
</table>

| Corrected serum calcium, mean (SD), mg/dL     | 9.2 (0.4) | 9.2 (0.4) |

<table>
<thead>
<tr>
<th>25-hydroxyvitamin D</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed, mean (SD), ng/mL&lt;sup&gt;c&lt;/sup&gt;</td>
<td>25.5 (9.5)</td>
<td>25.2 (9.4)</td>
</tr>
<tr>
<td>&lt;20 ng/mL, observed, No. (%)</td>
<td>746 (29.2)</td>
<td>788 (30.9)</td>
</tr>
<tr>
<td>&lt;20 ng/mL, deseasonalized, No. (%)</td>
<td>612 (23.9)</td>
<td>658 (25.8)</td>
</tr>
</tbody>
</table>

<sup>a</sup> percent do not add to 100.0% because of missing/don’t know responses.

<sup>b</sup> ≤600 IU per day if aged 50-70 years; ≤800 IU per day if aged 71-84 years.

<sup>c</sup> conversion to SI units: 1 ng/mL = 2.496 nmol/L
Table 2: Number of cancer registrations and deaths during follow-up to 31 December 2015, by type of cancer.

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Alive at 31 December 2015</th>
<th>Deaths</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First cancer registration</td>
<td>Cancer registration</td>
<td>Cancer registration</td>
</tr>
<tr>
<td></td>
<td>AFTER randomisation</td>
<td>AFTER randomisation</td>
<td>BEFORE randomisation</td>
</tr>
<tr>
<td><strong>Invasive neoplasms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>28</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Oropharynx &amp; Other digestive tract</td>
<td>17</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>Respiratory &amp; Intrathoracic organs</td>
<td>9</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Malignant melanoma &amp; Other malignant neoplasm of skin</td>
<td>50</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Breast</td>
<td>31</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Prostate</td>
<td>56</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Lymphoid &amp; Hematopoietic</td>
<td>25</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>17</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td><strong>In situ neoplasms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma in situ</td>
<td>71</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other carcinoma in situ</td>
<td>11</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>315</td>
<td>60</td>
<td>29</td>
</tr>
</tbody>
</table>
Table 3: Proportion of participants having incident cancer (C00-D09), or dying from cancer, during follow-up, and hazard ratios (placebo as reference) adjusting for age, sex (as appropriate), and ethnicity, by study treatment group.

<table>
<thead>
<tr>
<th>Cancer outcome</th>
<th>Vitamin D (n=2,558)</th>
<th>Placebo (n=2,550)</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
<th>P-value (Wald X^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N of events (%)</td>
<td>N of events (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary outcome: cancer registration from randomization to 31 July 2015</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All participants^a</td>
<td>165 (6.5)</td>
<td>163 (6.4)</td>
<td>1.01 (0.81, 1.25)</td>
<td>0.95</td>
</tr>
<tr>
<td>Males</td>
<td>108 (7.2)</td>
<td>110 (7.6)</td>
<td>0.96 (0.74, 1.25)</td>
<td>0.76</td>
</tr>
<tr>
<td>Females</td>
<td>57 (5.5)</td>
<td>53 (4.9)</td>
<td>1.09 (0.75, 1.59)</td>
<td>0.66</td>
</tr>
<tr>
<td>25(OH)D &lt;20 ng/mL^b</td>
<td>37 (6.0)</td>
<td>42 (6.4)</td>
<td>1.01 (0.65, 1.58)</td>
<td>0.96</td>
</tr>
<tr>
<td>25(OH)D ≥20 ng/mL^c</td>
<td>128 (6.6)</td>
<td>121 (6.4)</td>
<td>1.04 (0.81, 1.33)</td>
<td>0.79</td>
</tr>
<tr>
<td>Secondary outcomes for all participants</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer registration: randomization to 31 December 2015</td>
<td>188 (7.4)</td>
<td>187 (7.3)</td>
<td>1.00 (0.82, 1.22)</td>
<td>0.99</td>
</tr>
<tr>
<td>Cancer deaths: randomization to 31 December 2015</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer registration after randomization^d</td>
<td>30 (1.2)</td>
<td>30 (1.2)</td>
<td>0.99 (0.60, 1.64)</td>
<td>0.97</td>
</tr>
<tr>
<td>All cancer deaths^e</td>
<td>44 (1.7)</td>
<td>45 (1.8)</td>
<td>0.97 (0.64, 1.47)</td>
<td>0.89</td>
</tr>
<tr>
<td>Cancer registration: one year after randomization to:^f</td>
<td>31 July 2015</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>116 (4.6)</td>
<td>122 (4.9)</td>
<td>0.95 (0.74, 1.23)</td>
<td>0.69</td>
</tr>
<tr>
<td></td>
<td>31 December 2015</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>139 (5.6)</td>
<td>146 (5.8)</td>
<td>0.95 (0.75, 1.19)</td>
<td>0.64</td>
</tr>
<tr>
<td>Non-skin cancer registration: randomization to 31 July 2015^g</td>
<td>111 (4.4)</td>
<td>111 (4.5)</td>
<td>0.99 (0.76, 1.29)</td>
<td>0.96</td>
</tr>
<tr>
<td>Invasive cancer registration: randomization to 31 July 2015^h</td>
<td>128 (5.1)</td>
<td>131 (5.2)</td>
<td>0.97 (0.76, 1.24)</td>
<td>0.80</td>
</tr>
</tbody>
</table>

^a Includes 58 deaths due to cancer (28 in vitamin group and 30 in placebo group)
^b Based on deseasonalized concentrations – denominator: vitamin D = 612 participants, placebo = 658.
^c Denominator: vitamin D = 1946, placebo = 1892.
^d Denominator: vitamin D = 2544, placebo = 2535. Excludes those who died from cancer that was diagnosed before randomization.
^e Includes 29 deaths from cancer diagnosed before randomization (14 in vitamin D group and 15 in placebo group).
^f Denominator: vitamin D = 2504, placebo = 2504. Excludes those who were registered with cancer within 12 months of randomization.
Excludes malignant melanoma, other malignant neoplasm of skin and melanoma in situ.

Excludes in situ neoplasms.
Figure 1:

8,851 Assessed for eligibility

3,601 Excluded
1,087 Not interested
541 Too high vitamin D dose
497 Kidney stones
1,476 Other reasons

5,250 Baseline assessment

140 Excluded
92 Failed run-in
31 High calcium
17 Other reasons

5,110 Randomized

2,558 Randomized to vitamin D3
2,513 Confirmed starting vitamin D3 within two months

0 Excluded (withdrew consent)

By 1 year after randomization
6 Died (1 with cancer)
48 Incident cancer & alive
2,504 Alive & no incident cancer (included in >1 year analysis)

By 31 July 2015
59 More died
2,493 Alive
2,177 Participating (returned final or penultimate questionnaire)

By 31 December 2015
10 More died
2,483 Alive

2,558 Included in primary analysis

2,552 Randomized to placebo
2,491 Confirmed starting placebo within two months

2 Excluded (withdrew consent)

By 1 year after randomization
9 Died (4 with cancer)
37 Incident cancer & alive
2,504 Alive & no incident cancer (included in >1 year analysis)

At 31 July 2015
49 More died
2,492 Alive
2,138 Participating (returned final or penultimate questionnaire)

By 31 December 2015
22 More died
2,470 Alive

2,550 Included in primary analysis
Figure 2: Proportion (95% CI) of participants developing cancer during follow-up to 31 July 2015, by study group.

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1 year</th>
<th>2 years</th>
<th>3 years</th>
<th>4 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D</td>
<td>2558</td>
<td>2504</td>
<td>2453</td>
<td>1760</td>
<td>374</td>
</tr>
<tr>
<td>Placebo</td>
<td>2550</td>
<td>2504</td>
<td>2447</td>
<td>1899</td>
<td>275</td>
</tr>
</tbody>
</table>
By 1 year after randomization 6 Died (1 with cancer) 48 Incident cancer & alive 2,504 Alive & no incident cancer (included in >1 year analysis)

By 1 year after randomization 9 Died (4 with cancer) 37 Incident cancer & alive 2,504 Alive & no incident cancer (included in >1 year analysis)

By 31 July 2015 59 More died 2,493 Alive 2,177 Participating (returned final or penultimate questionnaire)

At 31 July 2015 49 More died 2,492 Alive 2,138 Participating (returned final or penultimate questionnaire)

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2,558 Included in primary analysis

2,550 Included in primary analysis