Vitamin D intake and breast cancer risk: a case–control study in Italy

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Background: Vitamin D has been suggested to play a protective role against several cancers, including breast cancer.

Patients and methods: We used data from a case–control study conducted in Italy from 1991 to 1994 to study the relation between dietary intake of vitamin D and breast cancer risk. Subjects were 2569 women with incident, histologically confirmed breast cancer and 2588 hospital controls. Odds ratios (ORs) and 95% confidence intervals (CIs) according to deciles of vitamin D intake were estimated by multiple logistic regression models.

Results: After allowance for major risk factors for breast cancer and dietary covariates including calcium and energy intake, there was no association with vitamin D up to the seventh decile. Thereafter, the OR declined, so that the overall trend was statistically significantly inverse. The OR for subjects in the three highest deciles of consumption compared with those in the lowest ones combined was 0.79 (95% CI 0.70–0.90). Intake of vitamin D >3.57 μg or 143 IU appeared to have a protective effect against breast cancer. The inverse association was consistent across strata of menopausal status.

Conclusions: This study adds to the existing evidence that vitamin D intake is inversely associated with breast cancer risk.

Key words: breast cancer, case–control study, risk factors, vitamin D

introduction

The hypothesis that vitamin D has a favorable effect on cancer risk was proposed in the early 1980s [1], but vitamin D started to be intensively studied in relation to cancer only in the 1990s [2]. Inverse associations have also been reported between vitamin D and risk of colorectal and prostate cancer, while the relations with other cancers have been less extensively studied [3].

With respect to breast cancer, at least four studies have considered serum or plasma vitamin D levels [4–7], with inconsistent results. Results from a pooled analysis of two studies reporting data on serum 25(OH)D and breast cancer, one from the UK [7] and one from the United States [6], indicated that subjects with serum 25(OH)D >50 ng/ml had a significant 50% lower risk of breast cancer compared with women having serum values <13 ng/ml [8].

At least six case–control studies [9–14] and six cohort studies [15–20] have reported data on various measures of dietary or supplemental intake of vitamin D and breast cancer risk. Of these, eight studies reported relative risks (RRs) below unity (significant for three cohort studies [16, 19, 20] and one case–control study [14]), two no association, and one a nonsignificant excess risk [11]. A randomized trial of supplemental calcium plus 1100 IU vitamin D3, which included 1179 postmenopausal women, reported a RR of 0.5, of borderline significance, for cancer incidence overall after 4 years, but the number of breast cancer cases was small (15 in the placebo, nine in the calcium and vitamin D group), and subjects that received calcium only had a similar reduction in breast cancer risk as those receiving calcium plus vitamin D [21].

To provide further information on the issue, we considered data on dietary vitamin D and breast cancer risk from a large multicenter case–control study in Italy. Findings on other micronutrients from the same dataset have been reported previously [22].
patients and methods

We conducted a multicentric case–control study of breast cancer from June 1991 to April 1994 in six Italian areas: the provinces of Pordenone and Gorizia, the greater Milan area, the urban area of Genoa, the province of Forli, the province of Latina, and the urban area of Naples [23]. Cases were 2569 women with incident, histologically confirmed breast cancer (median age 55, range 23–74 years) admitted to major teaching and general hospitals of the study areas. Controls were 2588 women (median age 56, range 20–74 years) with no history of cancer admitted to the same hospitals for acute, non-neoplastic, non-gynecological conditions, unrelated to hormonal or digestive tract diseases or to conditions linked to diet. Among controls, 22% had traumas, 33% other orthopedic diseases such as low back pain or strains, 15% acute surgical conditions, 18% eye diseases, and 12% other miscellaneous diseases. Less than 4% of cases and controls approached for interview did not consent to participate.

Cases and controls were interviewed in the hospital by centrally trained interviewers, using a standard structured questionnaire. This included information on sociodemographic factors, anthropometric variables, lifestyle habits, including tobacco smoking and alcohol drinking, as well as obstetric, gynecologic, and general medical history. A reproducible and valid [24, 25] food frequency questionnaire (FFQ) was used to assess the patients’ usual diet in the previous 2 years. The questionnaire included 78 foods or food groups, plus questions aimed at assessing fat intake and general dietary habits. Subjects were asked to indicate their average weekly consumption of single food items or food groups. Intakes lower than once a week, but at least once per month, were coded as 0.5/week. To compute energy and nutrient intakes, including vitamin D intake, an Italian food composition database as well as information from additional sources were used [22, 26, 27]. Use of vitamin supplements was uncommon in the early 90s in this population [22].

Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were estimated by modeling the data through logistic regression [28]. A core model was used that included age (quinquennia, categorically), study center (categorically), years of education (<7, 7–11, ≥12, categorically), age at menarche (in years, continuously), parity (0, 1, 2, 3, 4, 5), menopausal status (post- versus pre/perimenopausal), combined vegetable and fruit consumption (quintiles, orderly), calcium, β-carotene, vitamin E, flavone, flavonol, and total energy intake (quintiles, orderly). Additional analyses were done separately for Southern/Northern Italy and pre/perimenopausal women, adjusting also for body mass index (BMI) (quintiles, orderly) and oral contraceptive use (ever versus never use), as well as for postmenopausal women, adjusting also for BMI (quintiles, orderly), age at menopause (in years, continuously), and hormone replacement therapy (ever versus never). In order to provide more detailed analyses of the levels of vitamin D intake, vitamin D was entered in the models as deciles of intake (on the basis of case and control combined distribution) [29], or as a continuous variable, with the increment set at 1 standard deviation of the overall distribution. Tests for trends for deciles of vitamin D were on the basis of a likelihood ratio test between the models with and without a linear term for the vitamin D deciles.

results

Table 1 shows multiple logistic regression-derived ORs and corresponding 95% CIs for breast cancer according to intake (deciles) of vitamin D for three different models. In all models, no trend is noted up to the seventh decile. Thereafter, however, the OR declines, so that in models II and III, which generate more valid estimates for vitamin D intake in relation to breast cancer risk, the inverse trend over all deciles becomes statistically significant or borderline so. Since only intake of

<table>
<thead>
<tr>
<th>Vitamin D Deciles of intake, a</th>
<th>OR (95% CI)</th>
<th>P-value</th>
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<tbody>
<tr>
<td><strong>Model I</strong></td>
<td></td>
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<tr>
<td>Case controls</td>
<td></td>
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<tr>
<td>Upper cut point (g)</td>
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<tr>
<td>1.0</td>
<td>1.00 (0.69–1.45)</td>
<td>0.96 (0.60–1.57)</td>
</tr>
<tr>
<td>2.0</td>
<td>1.02 (0.68–1.51)</td>
<td>0.95 (0.60–1.57)</td>
</tr>
<tr>
<td>3.0</td>
<td>1.05 (0.70–1.56)</td>
<td>0.92 (0.60–1.57)</td>
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<tr>
<td>4.0</td>
<td>1.07 (0.71–1.60)</td>
<td>0.91 (0.60–1.57)</td>
</tr>
<tr>
<td>5.0</td>
<td>1.09 (0.72–1.65)</td>
<td>0.91 (0.60–1.57)</td>
</tr>
<tr>
<td>6.0</td>
<td>1.11 (0.74–1.65)</td>
<td>0.92 (0.60–1.57)</td>
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<tr>
<td>7.0</td>
<td>1.13 (0.75–1.65)</td>
<td>0.92 (0.60–1.57)</td>
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<tr>
<td>8.0</td>
<td>1.15 (0.76–1.65)</td>
<td>0.92 (0.60–1.57)</td>
</tr>
<tr>
<td>9.0</td>
<td>1.17 (0.77–1.65)</td>
<td>0.92 (0.60–1.57)</td>
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<tr>
<td>10.0</td>
<td>1.19 (0.78–1.65)</td>
<td>0.92 (0.60–1.57)</td>
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Table 1. Multiple logistic regression-derived OR and corresponding 95% CI for 2989 cases of breast cancer and 2888 controls, according to intake deciles of vitamin D (Italy, 1992–1994)

aDeciles among cases and controls combined.
bEstimated for an increment of intake equal to 1 standard deviation among cases and controls (=3.14 µg).
cReference category.
dAdjusted for age, study center, and education.
eAdjusted as in model I, controlling also for parity, age at menarche, menopausal status, and total energy intake.
fAdjusted as in model II, controlling also for vegetable and fruit consumption, calcium, β-carotene, vitamin E, flavone, flavonol, and total energy intake.
vitamin D after the seventh decile (>3.57 μg or 143 IU) appears to have a ‘favourable effect’ against breast cancer, which is significant above the ninth decile (>4.76 μg or 188 IU), indicating a threshold effect, we have also computed the ORs for subjects in the three upper deciles of consumption compared with those in the seven lower ones combined. The ORs from models II and III were, respectively, 0.75 (95% CI 0.66–0.85) and 0.79 (95% CI 0.70–0.90). In Table 2, the relation between vitamin D and breast cancer risk is presented in strata of menopausal status (adjusting also for BMI and some reproductive factors, as appropriate) and geographical area of origin. The inverse association between vitamin D intake and breast cancer risk is apparently more evident among women from Southern Italy compared with women from the North. However, when vitamin D was assessed as a continuous variable for all women, the P value for the interaction of vitamin D and geographical area of origin was 0.15. No substantial differences were observed across strata of menopausal status. In order to provide more stable estimates, we have also reported a comparison between deciles 8–10 combined and deciles 1–7 among these strata. The ORs were 0.80 (95% CI 0.64–0.99) and 0.78 (95% CI 0.66–0.92) among pre/perimenopausal and postmenopausal women, respectively, and 0.82 (95% CI 0.71–0.96) and 0.64 (95% CI 0.48–0.86) among women from Northern and Southern Italy, respectively.

discussion

In this large multicenter case–control study, dietary intake of vitamin D was inversely associated with breast cancer risk, after allowance for major recognized risk factors for breast cancer and several dietary covariates including energy intake. The inverse relation appeared to be restricted to the three highest deciles of vitamin D. The present study results support the existing evidence that increased levels of dietary intake of vitamin D are associated with decreased breast cancer risk [3, 8, 14, 30].

We collected information only on dietary sources of vitamin D. Our FFQ was tested for reproducibility [31] and validity [25]. Although at that time we had no information on vitamin D, the Pearson correlation coefficients for most micronutrients ranged between 0.6 and 0.7 for reproducibility and 0.4 and 0.5 for validity. The absence of data on supplement use is not a major problem, given the low frequency of supplement use by this Italian population in the early 90s [22]. Skin synthesis is, however, a major source of vitamin D [32]. Consequently, the absence of information on sun exposure or serum level of 25(OH)D is a limitation of the study. However, sun exposure is limited in winter, particularly among the elderly. In a study of plasma vitamin D and colorectal cancer risk, average UV sunlight exposure was less strongly correlated with 25(OH)D concentrations than vitamin D from nutrition and dietary sources [33]. Among the strengths of this study are the large dataset, the use of a reproducible and valid FFQ [24, 25], and the virtually complete participation of cases and controls. With reference to confounding, we were able to adjust for major recognized risk factors for breast cancer, and the study has generated results on other breast cancer risk factors that were consistent with earlier and subsequent investigations, providing assurance that major biases were not operating during implementation of the study. Allowance for intake of other micronutrients that were inversely associated with breast cancer in this dataset [22] did not change the association with vitamin D. The main dietary sources of vitamin D in this population were fish (55.0%), meat (23.5%), cheese (6.8%), and eggs (5.6%). Of these, fish was found to have an inverse association with breast cancer in our data, while some varieties of meat were positively associated [23]; no association was found with cheese and eggs.

The inverse association between vitamin D and breast cancer was consistent among strata of menopausal status and geographical area of origin, although appeared more pronounced in Southern compared with Northern Italy. This could be due to chance given the low number of subjects from Southern Italy, and the absence of significant

<table>
<thead>
<tr>
<th>Vitamin D</th>
<th>Cases : Controls&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Decile of intake, OR (95% CI) versus the lowest decile of intake&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Continuous OR (95% CI)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Menopausal status</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pre/perimenopause</td>
<td>987 : 842</td>
<td>0.76 (0.48–1.22)</td>
<td>0.85 (0.53–1.36)</td>
</tr>
<tr>
<td>Postmenopause</td>
<td>1579 : 1746</td>
<td>1.01 (0.73–1.39)</td>
<td>0.94 (0.68–1.29)</td>
</tr>
<tr>
<td>Geographical area</td>
<td></td>
<td></td>
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<tr>
<td>Northern</td>
<td>2024 : 2106</td>
<td>1.12 (0.83–1.50)</td>
<td>1.08 (0.81–1.45)</td>
</tr>
<tr>
<td>Southern</td>
<td>543 : 482</td>
<td>0.41 (0.22–0.76)</td>
<td>0.41 (0.22–0.76)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Adjusted for age, study center, education, parity, age at menarche, body mass index, oral contraceptive use (only pre/perimenopausal), age at menopause (only postmenopausal), hormone replacement therapy (only postmenopausal), vegetable and fruit consumption, calcium, β-carotene, vitamin E, flavone, flavonol, and total energy intake.

<sup>b</sup>Deciles among cases and controls combined.

<sup>c</sup>Estimated for an increment of intake equal to 1 standard deviation (1.34 μg).

<sup>d</sup>Z<sub>1</sub>, for interaction = 2.05 (P value = 0.15).

OR, odds ratio; CI, confidence interval.

<sup>e</sup>Strata do not add up to the total because of missing values.
heterogeneity. When the OR estimates were computed in the three upper deciles of consumption compared with those in the seven lowest ones combined, the difference was attenuated. Furthermore, the geographic area of residence (Northern versus Southern Italy) may not be an optimal surrogate for UV-B radiation exposure. A recent study in Australia reported a relatively high prevalence of vitamin D insufficiency in winter and spring across a wide range of latitudes and suggested that season may be more important than latitudes in predicting variation in 25(OH)D levels, although both accounted for less than one-fifth of the variation [34].

Several mechanisms of action of vitamin D on breast carcinogenesis have been suggested. The 25(OH)D can inhibit cell proliferation, induce differentiation and apoptosis, and reduce angiogenesis as suggested by in vitro and animal studies [3, 35–38]. It has also been reported that seasonal variation of 25(OH)D may also be related to changes in mammographic density, a recognized indicator of breast cancer [39]. The observation that reduced risk is restricted to the highest levels of vitamin D intake can be explained in term of a threshold effect on substrate availability of 25(OH)D to the terminal ductal lobular unit of the breast [8].

Differences in dietary patterns associated with differences in vitamin D intakes may at least in part account for the inverse association observed. In this dataset, the animal and fish products and unsaturated fat and fiber were inversely related to breast cancer risk, while the starch-rich pattern was directly associated with it. [40] These uncertainties and cautions notwithstanding the observation that vitamin D is inversely related to breast cancer risk are consistent with the long recognized geographic patterns of breast cancer in Italy, which shows higher rates in the North and lower in the South where sun exposure, together with selected aspects of diet, contributes to higher availability of vitamin D [1, 41].

acknowledgements

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