Qualified Health Claims for Calcium and Colorectal, Breast, and Prostate Cancers: The U.S. Food and Drug Administration’s Evidence-Based Review

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In 2003, the United States Food and Drug Administration (FDA) received a health claim petition for calcium supplements and reduced risk of colorectal, breast, and prostate cancers. Health claims characterize the relationship between a substance (food or food component) and disease (e.g., cancer or cardiovascular disease) or health-related condition (e.g., hypertension) and require premarket approval for the labeling of conventional foods and dietary supplements by the FDA. This review describes how the FDA used the evidence-based review system to evaluate the scientific evidence for these proposed health claims. FDA found no credible evidence to support health claims for calcium and a reduced risk of breast and prostate cancers. The agency did find limited evidence for the relationship between calcium intake and colorectal cancer risk.

INTRODUCTION

Emerging evidence on nutrition and health relationships in the late 1980s sparked the enactment of the Nutrition Labeling and Education Act (NLEA) of 1990 (1). NLEA allowed the United States Food and Drug Administration (FDA or the agency) to authorize health claims. Prior to 1990, no claims about disease were allowed on the food label. Health claims characterize the relationship between a substance (food or food component) and disease (e.g., cardiovascular disease) or health-related condition (e.g., hypertension) and require premarket approval for the labeling of conventional foods and dietary supplements by the FDA. NLEA allowed the agency to authorize health claims that met the significant scientific agreement standard. The significant scientific agreement standard provides strong evidence for the substance–disease relationship, is supported by the totality of publicly available data, and agreed on among qualified experts that the relationship is valid. In contrast to a significant scientific agreement (authorized) health claim, qualified health claims rely on less scientific evidence and are accompanied by disqualifying language to reflect the level of science supporting the claim. Qualified health claims were issued for the labeling of dietary supplements after several court decisions regarding First Amendment issues and later expanded to conventional foods due to a major initiative by the FDA in 2003 (2). In the 1999 court ruling, Pearson v. Shalala (3) concluded that the First Amendment protection of commercial speech does not permit the agency to reject health claims that it determines to be potentially misleading. The agency may add a disclaimer statement to the health claim (i.e., qualified health claim) to reflect the level of science unless the agency also reasonably determines that no disclaimer would eliminate the potential deception (4). Both authorized and qualified health claims require an extensive scientific review of the evidence. In July 2007, the agency released the draft guidance document, http://www.cfsan.fda.gov/~dms/hclmgui5.html (5), outlining the evidence-based review system for health claims. The evidence-based review system is a systematic process for evaluating the scientific evidence for proposed health claims. This review demonstrates how the agency evaluated the scientific evidence using this system for the proposed qualified health claims for supplemental calcium intake and risk of colorectal, breast, and prostate cancers.

BACKGROUND

Colorectal, breast, and prostate cancers are 3 of the most commonly diagnosed forms of cancer in the United States (6). Nutrition and diet are thought to play a significant role in reduction of these types of cancer (6), and many nutrients including calcium have been evaluated for their potential protective effect. Increased calcium intake is associated with decreased risk of colorectal cancer as well as breast cancer in epidemiological, cellular, and animal studies (7–10). Calcium has been associated with increasing cellular differentiation and apoptosis in both normal and tumor cells (7). For colorectal cancer, calcium may
bind bile and fatty acids in the intestinal tract and thereby keep these compounds from damaging the intestinal mucosa. It has been hypothesized that calcium may affect cancer risk through the metabolism of vitamin D, particularly in breast cancer (8). In contrast to colorectal and breast cancer, some epidemiological evidence has suggested that calcium may actually increase prostate cancer risk (11).

In December 2003, the FDA received a petition for qualified health claims regarding calcium from dietary supplements and a reduced risk of colorectal, breast, and prostate cancers from a dietary supplement manufacturer. This review outlines how the agency evaluated the scientific evidence for the proposed qualified health claims.

THE QUALIFIED HEALTH CLAIM PETITION PROCESS

Qualified health claim petitions submitted to the agency must follow specific rules outlined in the Code of Federal Regulations (ref 101.14 and 101.70). These requirements include defining the substance(s), diseases, or health-related conditions; summary of the scientific data (both positive and negative); copies of all computerized literature searches performed by the petitioner; all information relied on to support the proposed health claim; as well as any data reporting adverse consequences. The agency acknowledges receipt of the petition within 15 days. Within 45 days of receipt, the FDA will file the petition, thereby making the contents of the petition public. At the time of filing, FDA will post the petition on the FDA Web page for a 60-day public comment period. During this time, written comments may be submitted to the agency. On or before 270 days after receipt of the petition, a final decision will be sent to the petitioner in the form of a letter as to whether the FDA intends to exercise enforcement discretion with respect to a qualified health claim or deny the petition. The letter will be posted on the FDA's Web site and in the docket. When a letter of enforcement discretion has been issued, the FDA does not intend to object to the use of the claim specified in the letter provided that the products that bear the claim are consistent with the stated criteria. Extensions beyond 270 days can be granted upon mutual agreement between the petitioner and the agency.

EVIDENCE-BASED REVIEW SYSTEM

In 2007, the FDA published draft guidance on the evidence-based review system for the scientific review of health claims (5). The evidence-based system reviews and rates the scientific evidence for a given substance–disease relationship (health claim). The FDA reviews studies submitted in petitions seeking health claims, and the petitioner is required to provide all evidence related to the health claim (e.g., supportive and not supportive). Through a literature search, the agency identifies any additional studies that are considered to be relevant to the petitioned health claims. The FDA focuses its review on reports of human intervention and observational studies. In addition to individual reports of human studies, the agency also considers other types of data and information in its review such as meta-analyses, review articles, and animal and in vitro studies. These other types of data and information may be useful to assist the agency in understanding the scientific issues about the substance, the disease or health-related condition, or both but cannot by themselves support a health claim relationship.

The FDA evaluates the individual reports of human studies to determine whether any scientific conclusions can be drawn from each study. The absence of critical criteria, such as a control group or statistical analysis, means that scientific conclusions cannot be drawn from the study (12). Studies from which the FDA cannot draw any scientific conclusions about the health claim relationship are eliminated from further review. Because health claims involve reducing the risk of a disease in people who do not already have the disease that is the subject of the claim, the FDA considers evidence from studies in individuals diagnosed with the disease that is the subject of the health claim only if it is scientifically appropriate to extrapolate to individuals who do not have the disease.

The FDA rates the remaining human intervention and observational studies for methodological quality. This quality rating is based on several criteria related to study design (e.g., use of a placebo control vs. a nonplacebo controlled group), data collection (e.g., type of dietary assessment method), the quality of the statistical analysis, the type of outcome measured (e.g., disease incidence vs. validated surrogate endpoint), and study population characteristics other than relevance to the U.S. population (e.g., selection bias and whether important information about the study subjects—e.g., age, smoker vs. nonsmoker—was gathered and reported).

Finally, the FDA evaluates the results of the remaining studies and the strength of the total body of publicly available evidence. The agency conducts this rating evaluation by considering the study type (e.g., intervention, prospective cohort, case control, cross-sectional), the methodological quality rating previously assigned, the quantity of evidence (number of the various types of studies and sample sizes), whether the body of scientific evidence supports a health claim relationship for the U.S. population or target subgroup, whether study results supporting the proposed claim have been replicated (13), and the overall consistency (14) of the total body of evidence. Based on the totality of the scientific evidence, the FDA determines whether such evidence is credible to support the substance–disease relationship. If there is credible evidence, the agency determines the qualifying language that reflects the level of scientific evidence to support the relationship.

SURROGATE ENDPOINTS FOR CANCER

Both significant scientific agreement and qualified health claims are directed toward risk reduction in the healthy U.S. population or a specific subpopulation (e.g., the elderly). The FDA uses surrogate markers for disease risk when they have been appropriately validated and are recognized by the National
Many intervention studies have used subjects that were diagnosed with colorectal cancer. Health claims characterize the relationship between a substance and a reduction in risk of contracting a particular disease in healthy people. The FDA may consider evidence from studies in individuals already diagnosed with a disease if it is scientifically appropriate to extrapolate to individuals who do not have the disease; however, this was not the case for subjects diagnosed with colorectal cancer.

2. The studies have not measured a validated surrogate endpoint for colorectal cancer and therefore have not provided evidence for colorectal cancer risk reduction. Several studies have measured fatty acid, bile acid, or water content of feces; ornithine decarboxylase activity; or colon/rectal cell proliferation. These have not provided evidence for the risk reduction of colorectal cancer.

3. Intervention studies have used supplemental calcium in combination with other vitamins (selenium, vitamin E, vitamin C, and β-carotene) or have used dairy products in lieu of supplemental calcium as the intervention. Foods and multinutrient dietary supplements contain not only calcium but also other nutrients that may be associated with the metabolism of calcium and/or the pathogenesis of colon/rectal polyp recurrence or colorectal cancer. Therefore, no scientific conclusions could be drawn from them about the relationship between calcium supplements and colorectal cancer.

4. Studies have been a republication or reanalysis of a study already being used to evaluate the proposed claim; therefore, these studies have provided no new scientific data.

5. Statistical analysis has not been conducted in the studies to determine if there was a difference between the treatment group and the control group. Statistical analysis is critical because it provides the comparison between subjects consuming calcium and those not consuming calcium to determine whether there is a reduction in cancer risk. Thus, when statistics have not been conducted, it is not possible to determine if there was a difference between the treatment and control groups.

Two intervention studies have evaluated the relationship between calcium intake and reduced risk of colorectal cancer (16,17). Both studies have received high methodological quality study ratings. The Calcium Polyp Prevention Study was a randomized double-blind intervention trial on 930 subjects with a recent history (previous 3 mo) of colon/rectal polyps (16). The mean age of the subjects was 61 ± 9 yr, and 70% of the subjects were men. Of the 930 subjects that underwent randomization, 832 completed the study follow-up of two colonoscopies, at one and four years after enrollment. After a 3-mo placebo run-in period, the subjects were randomized to receive 3 g/day of calcium carbonate (1.2 g/day of elemental calcium) or placebo until the completion of the study. The relative risk for developing a polyp between the first and second endoscopy while consuming the calcium supplement was 0.81 [with 95% confidence interval (CI) = 0.67–0.99], indicating a significant decrease.

Bonithon-Kopp et al. (17) was a randomized, double-blind, intervention trial on 665 subjects with a recent history of colon/rectal polyps. There were 3 groups in the study: subjects that received calcium gluconolactate and carbonate daily (2 g/day elemental calcium) \( (n = 218) \), subjects that received 3.5 g of fiber per day \( (n = 226) \), and subjects that received a placebo \( (n = 221) \). Approximately 60% of the subjects were males, and the average age for the intervention groups was 59 ± 11 yr.
approximately 59 yr. Both the calcium and placebo groups had a similar number of subjects complete the study: 176 for calcium and 178 for placebo. The adjusted relative risk for calcium supplementation and polyp recurrence in this study was 0.66 (95% CI = 0.38–1.17). Calcium supplementation did not significantly reduce colorectal polyp recurrence in this study.

Observational Studies

Most observational studies that have evaluated calcium and the risk of colorectal cancer have estimated calcium intake from either dietary or water intake. Scientific conclusions could not be drawn from these studies regarding supplemental calcium and colorectal cancer risk for the reasons discussed in the Dietary Calcium and Cancer Risk section.

Six prospective cohort studies have evaluated the relationship between supplemental calcium and risk of colon/rectal cancer (18–23). All 6 studies were considered to be of high methodological quality. The Flood et al. (18) study followed a cohort of 45,354 U.S. women for approximately 8.5 yr and identified 482 cases of colon/rectal cancer during the follow-up. Calcium supplement consumption (≥800 mg/day) was associated with a decreased risk of colon/rectal cancer (relative risk of 0.76, 95% CI = 0.56–0.98) (18).

The Cancer Prevention Study II Nutrition cohort consisted of approximately 126,000 U.S. males and females who completed a detailed questionnaire regarding different lifestyle and dietary habits in 1992–1993 (19). After 4 to 5 yr of follow-up, 683 cases of colorectal cancer were identified in the cohort. Calcium supplement use was associated with a reduced risk of developing colon/rectal cancer with a relative risk of 0.69 (95% CI = 0.49–0.96). However, when the cohort was stratified by gender, calcium supplementation had no significant effect on colon/rectal cancer incidence.

The Nurses Health Study and Health Professionals Follow-up study (87,988 females and 47,344 males, respectively) evaluated calcium intake and colon/rectal cancer risk over 10 to 16 years of follow-up, identifying 1,025 colon/rectal cancer cases (20). Current calcium supplement use was associated with a decreased risk of distal colon cancer incidence in a combined cohort analysis (relative risk of 0.69, 95% CI = 0.51–0.94 compared to nonsupplement users). When the cohorts were stratified by gender, calcium supplementation had no significant effect on distal colon cancer incidence. Calcium supplementation was not specifically evaluated in proximal colon cancer; however, total calcium intake (supplemental and dietary calcium combined) did not demonstrate any reduction in risk.

A cohort of 35,216 women from Iowa assessed calcium intake and colon cancer risk (21). The women completed a questionnaire regarding dietary and supplemental sources of calcium in 1986 and were followed for 9 yr, with 241 colon cancer cases identified. Supplemental calcium use was associated with a significantly reduced risk of colon cancer incidence (relative risk of 0.6, 95% CI = 0.4–0.9) in women without a family history of colon cancer. There was no beneficial relationship between calcium supplementation and colon/rectal cancer in women with a family history of colon cancer.

Two prospective studies have evaluated the association between calcium supplementation and polyp recurrence (22,23). Martinez et al. (22) was a secondary analysis of an intervention study initially designed to evaluate fiber intake and polyp recurrence. The primary intervention had no effect on polyp recurrence. The study followed 1,304 males and females for 3 yr. Calcium supplement use had no association with polyp recurrence (relative risk of 0.94, 95% CI = 0.67–1.33). Hyman et al. (23) performed a secondary analysis of an intervention trial designed to evaluate different antioxidant compounds (β-carotene, vitamins C and E) and polyp recurrence. The intervention had no effect on polyp recurrence. The study followed 864 subjects for 4 yr. There was no association between calcium supplement use and polyp recurrence (relative risk of 0.76, 95% CI = 0.42–1.38).

Five case-control studies of moderate methodological quality have evaluated the relationship between calcium supplement use and colon/rectal cancer risk (24–28). Marcus and Newcom (24) conducted a case-control study in 678 controls and 512 female colon/rectal cancer cases from the United States. Supplemental calcium intake had no significant association with colon or rectal cancer risk (odds ratio (OR) = 1.0, 95% CI = 0.7–1.6, and OR = 0.8, 95% CI = 0.5–1.6, respectively). White et al. (25) found no significant association between calcium supplement use and colon cancer risk in 444 cases and 427 controls from the United States. Neugut et al. (26) performed two different case-control studies in one publication; the first study compared 297 subjects newly diagnosed with polyps to 505 controls. There was no association between calcium supplement use and polyp occurrence (OR = 0.9, 95% CI = 0.2–4.0). The second case-control study contained 297 subjects with recurrent polyps and 347 controls (without recurrent polyps but have a history of polyps). There was no association between calcium supplement use and polyp recurrence (OR = 2.9, 95% CI = 0.6–9.5). Wheelan et al. (27) conducted a case-control study with 183 subjects diagnosed with recurrent colon/rectal polyps and 265 subjects without recurrent colon/rectal polyps. Supplemental calcium intake was associated with a decreased risk of polyp recurrence (OR = 0.51, 95% CI = 0.27–0.96). Peleg et al. (28) found no relationship between prescribed calcium supplement use and colon/rectal cancer risk in 93 colorectal carcinoma cases, 113 colorectal adenocarcinoma cases, and 186 or 226 controls from the United States (OR = 1.93 and 0.68, 95% CI = 0.81–4.62 and 0.24–1.89, respectively).

In summary, there were two intervention studies and six prospective observational studies that provided information about the relationship between supplemental calcium intake calcium and colon/rectal cancer risk reduction (Table 1). One intervention study reported a significant reduction in recurrent
TABLE 1
Studies reviewed for the qualified health claim for calcium supplements and a reduced risk of colorectal cancer*

<table>
<thead>
<tr>
<th>Author and Year Publication (Ref. No.)</th>
<th>Study Type</th>
<th>Study Location</th>
<th>No. Cases and Control Subjects</th>
<th>Results/Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baron et al., 1999 (16)</td>
<td>Intervention</td>
<td>United States</td>
<td>409 calcium supplements, 423 placebo controls</td>
<td>Adjusted RR for calcium supplementation and polyp recurrence = 0.81, 95% CI = 0.67–0.99</td>
</tr>
<tr>
<td>Bonithon-Kopp et al., 2000 (17)</td>
<td>Intervention</td>
<td>Europe</td>
<td>221 calcium supplements, 221 placebo control</td>
<td>Adjusted RR for calcium supplementation and polyp recurrence = 0.66, 95% CI = 0.38–1.17</td>
</tr>
<tr>
<td>Flood et al., 2005 (18)</td>
<td>Cohort</td>
<td>United States</td>
<td>482 cases, 45,354 women</td>
<td>&gt;800 mg calcium supplements per day, adjusted RR = 0.76 (95% CI = 0.56–0.98)</td>
</tr>
<tr>
<td>Sellers et al., 1998 (21)</td>
<td>Cohort</td>
<td>United States</td>
<td>212 cases, 35,216 women</td>
<td>&gt;500 mg calcium supplements per day, adjusted RR for women with no family history colon cancer = 0.6 (95% CI = 0.4–0.9); adjusted RR for women with a family history of colon cancer = 1.0 (95% CI = 0.5–2.1)</td>
</tr>
<tr>
<td>McCullough et al., 2003 (19)</td>
<td>Cohort</td>
<td>United States</td>
<td>683 cases, 60,866 males, 66,883 females</td>
<td>&gt;500 mg calcium supplements per day, adjusted RR = 0.56 (95% CI = 0.49–0.96)</td>
</tr>
<tr>
<td>Wu et al., 2002 (20)</td>
<td>Cohort</td>
<td>United States</td>
<td>1,025 cases, 47,344 males, 87,988 females</td>
<td>Compared never users to current users of supplemental calcium, adjusted RR for distal colon cancer = 0.69 (95% CI = 0.51–0.94)</td>
</tr>
<tr>
<td>Hyman et al., 1998 (23)</td>
<td>Cohort</td>
<td>United States</td>
<td>260 cases (polypl recurrence), 864 subjects</td>
<td>No calcium supplement use compared to some use, adjusted RR = 1.25 (95% CI = 0.78–2.01)</td>
</tr>
<tr>
<td>Martinez et al., 2002 (22)</td>
<td>Cohort</td>
<td>United States</td>
<td>639 cases (polypl recurrence), 1,304 subjects</td>
<td>&gt;200 mg calcium supplements per day, adjusted RR = 0.94 (95% CI = 0.67–1.33)</td>
</tr>
<tr>
<td>Marcus and Newcom, 1998 (24)</td>
<td>Case control</td>
<td>United States</td>
<td>348 colon cancer cases, 164 rectal cancer cases, 678 controls</td>
<td>≥800 mg calcium supplements per day, adjusted OR for colon cancer = 1.0 (95% CI = 0.7–1.6); adjusted OR for rectal cancer = 0.8 (95% CI = 0.5–1.6)</td>
</tr>
<tr>
<td>Neugut et al., 1996 (26)</td>
<td>Case control</td>
<td>United States</td>
<td>193 recurrent polyps, 347controls, 297 newly diagnosed polyps, 505 controls</td>
<td>Calcium supplement use versus non users; recurrent polyp adjusted OR males = 1.3 (95% CI = 0.6–2.8), females = 1.9 (95% CI = 1.0–3.8); incidence polyp adjusted RR males = 0.7 (95% CI = 0.3–1.6), females = 1.3 (95% CI = 0.8–2.1)</td>
</tr>
<tr>
<td>Whelan et al., 1999 (27)</td>
<td>Case control</td>
<td>United States</td>
<td>448 subjects with a history of adenoma, 183 recurrent adenoma, 265 no recurrence</td>
<td>Calcium supplement use vs. nonusers for adenoma recurrence, adjusted OR = 0.51 (95% CI = 0.271–0.962)</td>
</tr>
<tr>
<td>White et al, 1997 (25)</td>
<td>Case control</td>
<td>United States</td>
<td>444 colon cancer cases, 427 Controls</td>
<td>Compared non–calcium-supplement users to subjects consuming &gt;100 mg/day, adjusted RR = 0.78 (95% CI = 0.52–1.18)</td>
</tr>
</tbody>
</table>

*Abbreviations are as follows: RR, relative risk; CI, confidence interval; OR, odd ratio.
colon/rectal polyps after supplementation with 1.2 g/day of calcium (16). In contrast, the intervention study by Bonithon-Kopp et al. (17) reported no significant benefit of calcium supplementation. The Baron et al. (16) study included more subjects and had a longer follow-up time than Bonithon-Kopp et al. (17), which may have provided the study with more power (e.g., ability to detect a difference) to find a significant beneficial effect of supplemental calcium on colon/rectal cancer risk. Of the six prospectively designed observational studies, four reported some type of significant association between calcium supplements and the risk reduction of colon/rectal cancer (18–21), whereas two studies reported no association (22,23). The studies that have reported protective associations for supplemental calcium were the cohorts with the largest number of subjects that contained both genders and a broad age range of subjects. The effect of calcium intake on decreased colon/rectal cancer risk was modest, and the effect did not seem to increase after a threshold of calcium intake was achieved (20), thereby suggesting that larger study populations are needed to find a modest reduction in risk. Of the four case-control studies, three studies reported no association between calcium intake and colon/rectal cancer (24–26), and one study reported a protective association between calcium and colon/rectal cancer risk (27). Based on the above evidence, the FDA concluded that there was a low level of comfort that a relationship exists between supplemental calcium intake and a reduced risk of colon/rectal cancer.

**BREAST CANCER**

**Intervention Studies**

The FDA did not identify any intervention studies that evaluated the relationship between calcium and breast cancer risk.

**Observational Studies**

The FDA identified eight observational studies on calcium and risk of breast cancer, consisting of two prospective cohort studies (29,30) and six case-control studies (31–36). Seven of these studies measured calcium intake from estimated intake of foods. Scientific conclusions could not be drawn from these studies regarding supplemental calcium and breast cancer risk for the reasons discussed in the Dietary Calcium and Cancer Risk section above.

One cohort study evaluated the relationship between calcium supplements and breast cancer (29) and received a high methodological quality rating. The cohort study evaluated calcium supplement intake in 88,691 pre and postmenopausal female nurses, with 3,482 cases identified during follow-up. Calcium supplement use was not significantly associated with breast cancer incidence in either group of nurses. Premenopausal women consuming greater than 900 mg/day of supplemental calcium had a relative risk of 1.10 (95% CI = 0.81–1.50) for developing breast cancer compared to women not consuming supplements. Postmenopausal women consuming greater than 900 mg/day of supplemental calcium had a relative risk of 0.93 (95% CI = 0.81–1.08) for developing breast cancer compared to women not consuming calcium supplements. When supplemental calcium intake was stratified by dietary calcium intake, no significant association between supplemental calcium intake and breast cancer was found. The FDA concluded that there was no credible evidence to support a qualified health claim for supplemental calcium intake and breast cancer risk.

**PROSTATE CANCER**

**Intervention Studies**

One intervention study was found by the agency relating to calcium supplementation and prostate cancer risk (37). The report was designed to specifically evaluate the effect of supplemental calcium intake on colon/rectal polyp recurrence. Prostate cancer incidence was a secondary endpoint of the study. Because the study did not screen for prevalent cases of prostate cancer at the onset of the study, the results may be biased due to an uneven distribution of prevalent cases in the treatment vs. the placebo group. Because uneven distribution of important patient or disease characteristics between groups may lead to mistaken interpretation (12), scientific conclusions could not be drawn from this study about the relationship between calcium and reduced risk of prostate cancer.

**Observational Studies**

The FDA identified 13 observational studies on the relationship between calcium intake and prostate cancer. Ten studies estimated dietary calcium intake from food or water consumption (38–47) and scientific conclusions could not be drawn for the reasons discussed above in the Dietary Calcium and Cancer section.

One prospective cohort study evaluated the relationship between calcium intake and prostate cancer and was of high methodological quality (48). The cohort followed 47,781 men for 8 yr and evaluated the effect of supplemental calcium use in a stratified analysis with dietary calcium intake. During follow-up 1,792 incident prostate cancer cases were identified. This study reported that the group consuming the least amount of dietary calcium (<600 mg/day) and the highest calcium supplement intake (>900 mg/day) was associated with a significant increase in the risk of metastatic prostate cancer (relative risk of 3.6, 95% CI = 1.5–8.8). No stratified analysis of supplemental and dietary calcium use for total prostate cancer (metastatic and nonmetastatic prostate cancer) was evaluated. However, total calcium intake (supplemental and dietary combined) at the highest intake level (greater than 2 g/day) was significantly associated with an increased risk of prostate cancer.

Two case-control studies of high methodological quality evaluated the relationship between supplemental calcium intake and prostate cancer risk (49,50). Kristal et al. (49) was...
a case-control study that included 697 incident prostate cancer cases and 666 controls from the Seattle, Washington area. Calcium supplement use was not significantly associated with prostate cancer risk, even at the highest quartile of intake (OR = 1.25, 95% CI = 0.73–2.17). Kristal et al. (50) was a case control study with 605 cases of cancer and 592 controls that evaluated calcium intake from supplements in a stratified analysis with dietary calcium intake. Calcium intake from supplements did not significantly affect prostate cancer risk. Because there were no studies that supported the proposed qualified health claim, the FDA concluded that there was no credible evidence to support a relationship between the consumption of supplemental calcium and prostate cancer risk.

SUMMARY AND CLAIMS

The FDA concluded that there was no credible evidence to support qualified health claims about supplemental calcium intake and a reduced risk of breast or prostate cancers. However, FDA concluded that there was limited credible evidence for a qualified health claim about supplemental calcium intake and colon/rectal cancer, provided that the qualified health claim was appropriately worded so as to not mislead consumers. Thus, the agency issued a letter of enforcement discretion for the use of the following claim:

Some evidence suggests that calcium supplements may reduce the risk of colon/rectal cancer, however, FDA has determined that this evidence is limited and not conclusive.

New Research

Since the FDA issued a letter of enforcement discretion on calcium supplements and reduced risk of colorectal and breast cancers in 2005, several studies have been published (51–53). Grau et al. (51) continued to follow subjects from the Calcium Polyp Prevention Study [Baron et al. (16)] and reported a reduced risk in the recurrence of colorectal polyps existed in subjects receiving calcium supplements 5 yr after the intervention was stopped. A study by Lappe et al. (52) evaluated colon and breast cancer incidence as a secondary endpoint for an intervention study evaluating calcium supplement intake and fracture incidence in postmenopausal women. Because colon or breast cancer were secondary endpoints (52), the study would be similar to Baron et al. (37) that was discussed above and therefore would not be included in a future review. McCullough et al. (53) evaluated calcium supplement use and the risk of breast cancer in a cohort of 68,000 women and reported no association. These studies have not been evaluated using the FDA’s evidence-based review system; however, based on preliminary appraisal, they do not seem to contradict the conclusions made by the FDA based on the credible evidence used to evaluate the qualified health claims for calcium supplements and reduced risk of colorectal and breast cancers.

REFERENCES


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