Milk and the Risk and Progression of Cancer

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Abstract

Observational evidence suggests that nutritional factors contribute to a substantial proportion of cancer cases, and milk contains numerous bioactive substances that could affect risk and progression of cancer. Cancer results from multiple genetic and epigenetic events over time, so demonstrating a specific effect of nutrients or other bioactive food components in human cancer is challenging. Epidemiological evidence consistently suggests that milk intake is protective against colorectal cancer. Calcium supplements have been shown to reduce risk for recurrence of adenomatous polyps. Calcium supplementation has not been observed to reduce risk for colon cancer, although long latency and baseline calcium intake affect interpretation of these results. High calcium intake from both food and supplements is associated with increased risk for advanced or fatal prostate cancer. Results from epidemiological studies examining the relationship between intake of dairy foods and breast or ovarian cancer risk are not consistent. Animal studies have suggested that galactose may be toxic to ovarian cells, but results from epidemiological studies that have examined ovarian cancer risk and milk and/or lactose intakes are mixed. Dietary guidelines for cancer prevention encourage meeting recommended levels of calcium intake primarily through food choices rather than supplements, and choosing low-fat or nonfat dairy foods.

Introduction

Cancer is one of the leading causes of death worldwide, accounting for 7.6 million (13%) of all deaths according to World Health Organization statistics [1]. Notably, patterns of cancer, like dietary patterns, are highly variable across regions and countries with different levels of economic development [2]. Over the past 30 years, improvements have been observed in 5-year survival rates for all cancers combined and for several specific cancers in developed
Table 1. Bioactive food components in milk that have been suggested to affect risk and progression of cancer [2, 14–16]

<table>
<thead>
<tr>
<th>Class</th>
<th>Bioactive component</th>
</tr>
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<tbody>
<tr>
<td>Vitamins</td>
<td>Vitamin D in fortified products</td>
</tr>
<tr>
<td></td>
<td>Vitamin A (retinol, retinyl esters)</td>
</tr>
<tr>
<td>Minerals</td>
<td>Calcium</td>
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<tr>
<td></td>
<td>Magnesium</td>
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<tr>
<td>Macronutrients</td>
<td>Dietary fat</td>
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<tr>
<td></td>
<td>Conjugated linoleic acid</td>
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<tr>
<td></td>
<td>Galactose (from lactose)</td>
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<tr>
<td>Hormonal factors</td>
<td>Reproductive hormones</td>
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<tr>
<td></td>
<td>IGF-I</td>
</tr>
<tr>
<td>Probiotics and related factors</td>
<td>Lactic acid bacilli-produced butyric acid</td>
</tr>
<tr>
<td></td>
<td>Bifidobacteria in fermented products</td>
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<tr>
<td>Other constituents</td>
<td>Carotenoids (β-carotene)</td>
</tr>
<tr>
<td></td>
<td>Pesticides</td>
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</tbody>
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countries, attributed primarily to improved initial treatments and to increased screening that results in diagnosis at an earlier stage [3]. An increasing population of cancer survivors, i.e. individuals with a history of cancer who are thus at risk for recurrence or new cancers, has promoted increased interest in whether dietary factors may influence this risk and long-term survival [3, 4].

Accumulated data on diet and cancer over the past several decades suggest that approximately 30–40% of cancer cases are potentially preventable via food choices and the modification of nutritional factors [5]. Observed associations between dietary patterns and cancer mortality and morbidity have led to hypotheses about cause and effect relationships, which have often been examined more specifically in laboratory studies of biological activities of dietary constituents, case-control and cohort studies within populations, and clinical trials. Food provides nutrients and numerous other bioactive compounds, many of which have been linked specifically to cellular and molecular events and activities that have been identified in the development and progression of cancer [6]. Milk contains numerous bioactive substances that could potentially affect risk and progression of cancer (see table 1). The relationship between cancer risk and progression and the intakes of milk and/or these bioactive constituents has been the focus of epidemiological and clinical investigations.

**Key Issues in Diet-Cancer Research**

Examining the evidence linking milk intake to cancer risk and progression requires an appreciation of the multistage process of carcinogenesis. Cancer
results from multiple genetic and epigenetic events involving protooncogenes, tumor suppressor genes and antimetastasis genes throughout progression [7]. Clinical cancer is not determined by a single molecular event that disrupts normal cellular function or regulation of growth, but instead results from a series of disruptions across the cancer continuum. This continuum extends from the earliest cellular changes, to a preneoplastic lesion, to a malignant tumor, and finally, to metastasis. Genetic or inherited factors play a role in determining susceptibility to molecular and genetic changes in the process of carcinogenesis, although notably, nutritional factors appear to influence risk even in the presence of highly penetrant, dominant gene mutations [8]. Demonstrating a specific molecular effect of nutrients or other bioactive food components in human cancer, in which a series of genetic and epigenetic changes has occurred over years or decades, is logistically challenging.

Also, disentangling the effects of various foods, specific dietary constituents, and related lifestyle factors and characteristics (e.g. physical activity, obesity) that influence risk and progression of cancer has proven to be very challenging. The clustering of health-related behaviors, overall dietary pattern, and food choices is commonly observed [9], so attributing causality or protection to a specific dietary factor, such as milk intake, is limited by the possibility of confounding, especially in observational studies.

In general, interpretation of results from observational studies that rely on self-reported dietary data is particularly constrained by the problem of crude and imprecise methods that are used in the collection of these data, as well as a food content database that is often of limited quality. The use of suitable dietary biomarkers, rather than reliance solely on self-reported dietary intake data, is recognized increasingly as being of value for more accurately characterizing usual patterns of intake and true exposure [10].

Randomized clinical trials, especially those involving isolated dietary constituents as supplements, would seem to be a preferable approach to testing the specific effect of dietary factors on cancer risk and progression, but interpretation of the results of such studies in cancer prevention has been difficult. These studies have been relatively short-term in nature, especially in consideration of the long process and several genetic and molecular steps in the development of clinical cancer. As a specific example, there is a long latency associated with the development of colon cancer, so administering nutrients or other bioactive compounds and examining cancer outcomes in middle-aged and older individuals over a span of 5–7 years in a clinical trial does not address the possibility that a lifetime of high or low intake, or differential intakes at another point in the colon cancer continuum, might affect risk for cancer. Alternatively, many of these clinical trials have involved individuals with precursor lesions [11], such as clinical trials of the effect of calcium on risk for recurrence of colorectal adenomatous polyps. The rationale for using recurrence of colorectal adenomas as the primary end point is that adenomatous polyps are considered precursors of most cancers of the large
bowel, although most polyps do not progress to lesions. Thus, this approach does not truly address the possible effect on colon cancer outcomes.

Within these recognized constraints on interpretation and conclusions, available data and current evidence suggest a possible role for milk intake, or certain bioactive constituents of milk (e.g. calcium, vitamin D), in the etiology of cancer. Separating the effects of the intake of milk per se and bioactive components may not be possible or even necessary for translation into public health recommendations. For example, milk and other dairy foods are a rich source of dietary calcium. In countries in which milk and other dairy products are consumed, these foods are the major source of calcium, so evidence linking calcium intake to cancer is highly relevant to dietary recommendations regarding milk intake. Also, milk is an important source of dietary vitamin D in the US, Canada and other countries in which milk is fortified with this compound. Thus, milk intake is a potentially important determinant of vitamin D status depending on the national policies of vitamin D fortification and other factors that determine vitamin D status, such as sunlight exposure and skin pigmentation [12, 13].

**Colorectal Cancer**

Cancer of the colon is the fourth most commonly diagnosed cancer worldwide, and incidence rates have been increasing steadily, especially in developed countries [2]. In the US, colorectal cancer accounts for 10 and 11% of the incident cancer cases in men and women, respectively, and 10% of cancer deaths in both gender subgroups [3]. The World Health Organization statistics for colorectal cancer incidence worldwide indicate that incidence in the less developed countries is increasing dramatically [1, 14], with associated high mortality rates. Results from ecological and migrant studies have long suggested that diet is an important environmental factor that influences the risk and progression of colon cancer. Colon and rectal cancers have a well-established and defined continuum of cellular changes and associated lesions that appear to occur in the stepwise process of developing an invasive tumor.

Numerous observational epidemiological studies have examined the relationship between milk intake and risk for colorectal cancer, as summarized in several recent comprehensive reviews [2, 15, 16]. The vast majority of these observational studies, which include both cohort and case-control studies, have identified a protective effect of milk. For example, Cho et al. [17] conducted a large pooled analysis of data from ten cohorts (n = 534,536) from five countries, in whom 4,992 individuals were diagnosed with colorectal cancer at follow-up. Individuals who consumed more than a glass of milk (≥250 g/day) had a 15% reduced risk of developing colorectal cancer (relative risk, RR, 0.85; 95% confidence interval, CI, 0.78–0.94), compared to those who consumed <70 g/day. For each 500 g/day increase in milk intake, the risk of
colorectal cancer was reduced by 12% (RR 0.88, 95% CI 0.82–0.95). Few studies have examined whether the effects are similar across milk products containing higher versus lower levels of fat, which is relevant because of the potential adverse effect of dairy fat intake on cardiovascular disease risk, and possibly, risk for cancer. Data on the relationship between intakes of other dairy foods and colorectal cancer incidence are less consistent. In the large meta-analysis described above [17], relationships between colorectal cancer risk and intakes of other dairy products (measured in five of the ten cohorts) were inverse but not significant. Meta-analysis of studies that examined the relationship between intake of cheese, a dairy food which is typically high in fat, and colorectal cancer risk suggests an increased risk that was not significant [2, 16].

Similarly, calcium intake has been found to be inversely associated with reduced risk for colorectal cancer in the majority of observational studies. Cho et al. [17] found dietary calcium intake to be associated with a significantly reduced risk of colorectal cancer (RR 0.86, 95% CI 0.78–0.95 for the highest versus lowest intake group). In another meta-analysis of ten cohort studies that was conducted for the second World Cancer Research Fund (WCRF) report [2], the RR was 0.98 (95% CI 0.95–1.00) per 200 mg calcium/day. Both dietary calcium and total calcium intake (including supplements) have generally been observed to be protective in a dose-response manner up to a threshold of about 1,200–1,400 mg/day.

The effect of calcium supplementation on recurrence of adenomatous polyps and colon cancer incidence has been tested in a few clinical trials. In a randomized controlled trial of calcium (1,400–1,500 mg/day), calcium plus vitamin D or placebo conducted in postmenopausal women, total cancer incidence at all common cancer sites was significantly lower among the women taking calcium plus vitamin D, but the number of cases was so small that inferences about the effectiveness are unclear [18]. Among secondary outcomes in the Women’s Health Initiative (WHI) randomized controlled trial of calcium (1,000 mg/day) plus vitamin D or placebo, colon cancer incidence did not vary between the intervention and placebo groups over 7 years of follow-up [19]. Notably, these WHI participants reported a mean total calcium intake of 1,151 mg/day at baseline, and personal use of a calcium supplement was reported by 54% at baseline and 69% at follow-up clinic visits, with a similar usage pattern in treatment and control groups. In both of the two clinical trials that examined the effect of calcium supplementation on risk for recurrence of adenomatous polyps (reviewed in Weingarten et al. [20]), beneficial effects were observed. At doses of 1,200 and 2,000 mg/day for 3–4 years, a reduction in the risk for recurrent adenoma was observed (odds ratio, 0.74, 95% CI 0.58–0.95) when the results were combined. The beneficial effect of supplemental calcium was observed to be most important in individuals who had baseline levels of serum 25-hydroxyvitamin D that was above the median in one of these trials [14], supporting the synergistic effect of these compounds.
In numerous epidemiological studies, good vitamin D status (reflected in adequate levels of serum 25-hydroxyvitamin D) has been consistently linked with lower risk for colorectal cancer, as previously reviewed [14, 16].

Several mechanisms of action have been proposed to explain a protective effect of milk intake on colorectal cancer. Calcium influences cell growth and apoptosis and may also sequester tumor-promoting secondary bile acids in the intestine. Vitamin D has a demonstrated role in cell growth regulation via gene transcription, which affects differentiation and apoptosis, including the epithelium of the colon. Additional bioactive components of milk that may specifically affect colorectal cancer progression include magnesium, butyric acid produced by microflora, and conjugated linoleic acid, all of which have been observed to inhibit cell proliferation and tumor cell growth in laboratory studies [14–16].

**Prostate Cancer**

Cancer of the prostate is the most commonly diagnosed invasive cancer among men in most developed countries [2]. Worldwide, it is the second most common cancer in men, accounting for 12% of incidence cancer cases in men. In the US, it accounts for 33% of new cases [3], and approximately 9% of cancer deaths among men in the US are attributable to prostate cancer. Evidence from migrant populations supports the likelihood that environmental factors, such as diet, are among the important etiologic factors determining risk for prostate cancer.

As recently reviewed [2, 21], numerous observational epidemiological studies, including several meta-analyses, have examined whether milk, dairy foods and/or calcium are associated with risk for prostate cancer. In contrast to the evidence linking higher milk intake to reduced risk for colorectal cancer, the relationship between intake of milk and/or dairy foods and prostate cancer risk is suggestive of an adverse, rather than a protective, effect. The adverse effect is modest and considered suggestive rather than conclusive, as summarized in the WCRF second report [2]. For example, one recent meta-analysis of eleven cohort studies reported a summary RR of 1.11 (95% CI 1.03–1.19) per serving for total dairy foods, 1.06 (95% CI 0.91–1.23) for milk, and 1.11 (95% CI 0.99–1.25) for cheese, similar to results from other large cohorts and pooled studies [reviewed in 15, 21]. The most recent meta-analysis on eighteen cohort studies also found a slightly increased risk [22], although three of the five large cohort studies subsequently published found no strong evidence for the positive association between dairy food intake and prostate cancer risk. Some of these observational studies attempted to examine the effect of higher- versus lower-fat milk in the analysis, but a differential effect is not apparent based on data in the studies reported to date.
In comparison with the large number of epidemiological studies of diet and risk for incident prostate cancer, a limited number of investigations of the relationship between pre- and postdiagnostic diet and the risk of prostate cancer progression have been conducted. In a large US cohort, Chan et al. [23] identified 392 progression outcomes in 1,202 men diagnosed with incident localized/regional prostate cancer and found that milk intake was associated with a small elevation in risk (adjusted hazard ratio, 1.12 for one serving/day increase, p < 0.05).

A more consistent and stronger positive association between calcium intake, whether from dietary sources or supplements, and prostate cancer risk has been observed in these cohort studies and also case-control studies. For example, Giovannucci et al. [24] examined data from a large cohort (n = 51,529) and found calcium intake to be particularly associated with increased risk for fatal or advanced prostate cancer (RR 2.08, 95% CI 1.05–4.10), although the effect was not evident until the level of intake exceeded 1,000 mg/day. Notably, secondary analysis of data from one of the calcium supplementation trials aimed at reducing adenomatous polyp recurrence revealed a null or even inverse association between calcium supplementation and incident prostate cancer risk [25].

One proposed mechanism by which intakes of milk, dairy products and/or calcium have been suggested to affect prostate cancer is by downregulating the synthesis of 1,25-dihydroxyvitamin D, the bioactive vitamin D metabolite involved in regulating cellular differentiation and proliferation of prostate epithelia. However, a relationship between 1,25-dihydroxyvitamin D (or even 25-hydroxyvitamin D) in the circulation and prostate cancer risk has not been demonstrated, so this hypothesis is not well supported. Another hypothesis relates to circulating insulin-like growth factor (IGF)-I, which stimulates prostate cell growth and has been shown to be moderately increased by milk intake. However, circulating IGF-I concentration has not been consistently linked with increased prostate cancer risk, so this hypothesis also is not well supported by the evidence.

**Breast and Ovarian Cancer**

Carcinomas of the breast and ovary are hormone-related cancers that have biological similarities. Breast cancer is the most common invasive cancer among women worldwide, accounting for approximately 23% of all cancers in women [1, 2]. Rates are highest in more developed countries; for example, it accounts for 26% of new invasive cancer cases and 15% of cancer deaths in women in the US [3], and rates are increasing rapidly in middle- and low-income countries. Ovarian cancer is much less common than breast cancer but is more likely to have a worse prognosis. Rates are generally higher in more developed and high-income countries, with observed increases in incidence
in countries undergoing economic transition. Ovarian cancer accounts for 3% of incident cancers in women in the US but 6% of cancer deaths [3].

Estrogens are thought to play an important role in breast and ovarian cancers. Normal cell proliferation and differentiation in these tissues is highly responsive to estrogens and the other gonadal hormones, as well as cellular factors and mitogens that affect growth regulation and apoptosis and thus influence carcinogenesis in all cell types. In addition to the ovarian steroids, other growth factors and mitogens influenced by nutritional factors and dietary patterns also appear to play an important role in the initiation and promotion of breast cancer.

A small proportion of breast cancers can be linked to a specific inherited susceptibility, and inherited variations in genes relevant to biochemical or metabolic pathways involved in mammary cell biology also are likely to increase risk for breast cancer. The incidence of breast cancer varies widely by geographical location and with migration, suggesting that environmental factors, such as diet, contribute substantially to risk. Dietary factors are believed to influence the risk and progression of breast and ovarian cancer, either through effects on hormonal status or via direct tumor-promoting or anticarcinogenic effects.

Over the past several decades, numerous epidemiological studies have examined relationships between dietary intake of milk and dairy foods and the risk and progression of breast cancer. As previously reviewed [2, 15], results from these epidemiological studies have not consistently demonstrated an association between intake of dairy foods (high- or low-fat) and breast cancer risk. Instead, the overwhelming evidence suggests that adiposity, low levels of physical activity and weight gain during adulthood appear to be the most important diet-related determinants of risk, which is reflected in current recommendations for the prevention of breast cancer [2, 26].

Three randomized clinical trials have tested whether a change in diet composition (a reduction in fat intake, and in one study, increased vegetable, fruit and fiber intake) can affect primary breast cancer risk or recurrence and/or survival in women diagnosed with early stage breast cancer. In the WHI Dietary Modification Trial, 48,835 women were assigned to a low-fat dietary pattern or control group and followed for approximately 8 years, and no overall effect on incident cancer was observed [27]. Milk and dairy foods were among the foods targeted for reducing fat content, because these foods contributed 10% of total dietary fat at baseline. Although a change in total milk or dairy food intake was not encouraged, a change in the type of milk or dairy product was among the goals, and a reduction of –2.5 g fat/day from cheese at year one (and –2.4 g fat/day from cheese at year two) was observed in response to the intervention [28].

Two trials have tested whether diet modification following the diagnosis of early stage breast cancer affects cancer outcomes [29]. The Women's Intervention Nutrition Study (WINS) tested a low-fat diet (≤15% of energy
intake) in 2,437 postmenopausal women with early stage breast cancer. With a median follow-up of 5 years, the WINS intervention resulted in a difference in dietary fat intake (33.3 vs. 51.3 g fat/day in the intervention versus control groups at year one), which was associated with modest weight loss (averaging 2.7 kg) and a 24% reduction in new breast cancer events in the intervention group, although a stronger protective effect (42% reduction) was observed in the subgroup of women with estrogen receptor-negative tumors. The Women's Healthy Eating and Living (WHEL) Study tested the effect of a diet very high in vegetables, fruit, and fiber and low in fat (20% of energy intake) on prognosis in 3,088 pre- and postmenopausal breast cancer survivors who were followed for an average of 7.3 years. At baseline, the WHEL Study participants reported an average intake of 7.3 servings/day of vegetables and fruit, which averaged 9.2 in the intervention group and 6.2 in the control group at 6 years. Recurrence-free survival did not differ across the two study arms. In that study, serum estrogen at baseline was found to be independently associated with poor prognosis, and a protective effect of the diet was observed in the subgroup of women who did not report hot flashes at enrollment. These findings suggest that reproductive hormone status may determine whether a high-vegetable, fruit and fiber diet may improve prognosis. Another finding from the WHEL Study was that total exposure to carotenoids over the course of the study, which was largely determined by the level at enrollment, was associated with breast cancer-free survival regardless of study group assignment. In additional subsequent analysis, milk consumption (a variable that combined milk, cream, and yogurt) at year one was observed to be slightly higher in the intervention versus control group (a difference of 0.1 serving/day) but unrelated to breast cancer-free survival in a Cox proportional hazards model controlled for stage, grade, ethnicity, and age.

The relationship between vitamin D status and breast cancer is an area of current interest, because several epidemiological studies have linked lower serum 25-hydroxyvitamin D levels with higher risk for breast cancer [30]. Notably, results from the WHI supplement study revealed no effect of calcium or calcium plus vitamin D supplements on breast cancer risk [31].

Although fewer epidemiological studies have been reported for ovarian cancer than for breast cancer, the available evidence for a relationship with intake of milk or dairy foods and cancer risk is not consistent [reviewed in 2, 15]. A possible role for intake of lactose (or more specifically, galactose, a unique monosaccharide constituent of lactose) in the development of ovarian cancer has been the focus of some research. The suggestion was based on animal studies showing that a diet very high in galactose is toxic to oocytes and evidence that the genetic disorder of galactosemia causes premature ovarian failure in women. A few case-control and cohort studies have investigated this relationship, and the results are mixed. In one follow-up study of the influence of dietary factors on survival in a group of 609 women who had been diagnosed with ovarian cancer, lactose intake was found to be modestly
associated with mortality (hazard ratio 1.32, 95% CI 0.99–1.75 for the highest versus lowest tertile), although an association between intake of total dairy products and survival was not evident [32].

**Conclusions**

Currently, the weight of the evidence suggests that intake of milk and/or constituents such as calcium and vitamin D may influence the risk and progression of large bowel (colon and rectum) and prostate cancer, while the evidence is mixed or lacking for other cancers. The WCRF report concluded that there is a probable link between milk intake and colorectal cancer in decreasing risk, and a probable link between diets high in calcium and prostate cancer in increasing risk [2]. In the WCRF personal recommendations, milk or dairy food intake is not specifically addressed, although meeting nutritional needs through foods is encouraged and dietary supplements are not recommended for cancer prevention. The current American Cancer Society guidelines for cancer prevention advise individuals to consume recommended levels of calcium intake, primarily through food choices (rather than supplements), and that people who obtain much of their calcium intake from dairy products should select low-fat or nonfat choices [26]. These strategies are consistent with general public health guidelines to promote good health and reduce risk for chronic disease.

**References**

Milk and Cancer


Discussion

Dr. Gibson: I was wondering whether milk is a biomarker for some other dietary habits or lifestyle or whatever in the same way that smoking often is. I mean smoking isn't healthy, I understand that, but it often coincides with low socioeconomic status.
So, to what extent do you feel that the milk situation is actually representing something else?

Dr. Rock: That’s a good question, and that’s why I am talking about different quality of studies that are done; it’s because we try to identify those components. I examined the data in the Women’s Healthy Eating and Living study to see if milk or dairy products were associated with a risk of recurrence in those women. The relationship was not linear, with grade and stage being the primary predictors. Ethnicity confounds the relationship because the Asian-American women in that study had much lower risk for recurrence, and they represent a group that consumes lower amounts of milk. Another interesting point is that the more we learn about bioactive ingredients in food, the more we need to do adjusting, for example soy and genistein have been shown to actually reduce the effect of that CYP24 that degrades the vitamin D active compounds.

Dr. Melnik: I would like to hear your opinion concerning high progesterone levels in the fraction of milk lipids due to the technique of milk production by permanently pregnant cows. According to my calculations, heavy meals including the intake of butter, cream and cheese could result in a daily ingestion of about 50 µg of progesterone. So, this is in the range of an oral contraceptive. This may have an effect on fertility. Furthermore, progesterone is an important hormone involved in the pathogenesis of breast cancer [1].

Dr. Rock: There are two things that make me worry less than you. We know for example the soy estrogens have such low affinity with binding to estrogen receptors so that they really only get important in older women. There is little competition against the natural endogenous hormones. It is important to look for consistency across different types of studies: if they were that bad, we would see an adverse effect of milk and dairy food intake on breast cancer incidence and progression, and that just hasn’t emerged. So I am not concerned about that for that reason. People are getting carried away by vitamin D right now, especially in the countries where milk is the major source of vitamin D. I think we should just wait and see because that’s a vitamin that clearly at high amounts is associated with adverse effects. In the ATBC study, with 29,000 Norwegian men, higher vitamin D in the blood was actually associated with a much higher risk for pancreatic cancer, which is a problem in smokers in particular; that’s a cancer that is driven by smoking.

Dr. Martin: You nicely explain the problems with epidemiology. In fact, one of our doctors in the UK who writes for *The Times* once wrote that the best thing that we could do for public health is to close all departments of epidemiology. So I wondered whether we should focus on randomized controlled trials instead. Specifically, whether we should focus on primary or secondary prevention trials, particularly since you showed that dietary modification in primary intervention trials is almost impossible, but secondary prevention trials can modify diet.

Dr. Rock: That’s a very good comment. I think epidemiology is a tool like biostatistics. It’s a source of hypothesis, and it’s people eating food, and usually we can follow them long enough to see cancer outcomes. The problem with clinical trials when you have a cancer outcome is that the expense is just phenomenal and that long latency with cancer makes it unlikely that funding for a clinical trial for 50 years to see who develops colon cancer would be achieved. Another really good point you brought up is to collect as much information as we can. In clinical trials, people can put away aliquots for future studies. As an example, I will be presenting an abstract in *Experimental Biology* this year showing that we were able to examine the effect of weight loss on plasma hydroxyvitamin D levels, because as Dr. Prentice mentioned, it’s usually lower in obese individuals, and we don’t know why. The question is when people lose weight, does it go up? So now in my weight loss studies completely unrelated to cancer, I can
get blood samples, and 20 years from now, if we have aliquots put away and there are emerging hypotheses of factors and mechanisms that can be explored, that's where we will get the most out of clinical trials.

Dr. Anderson: When you talked about epidemiology giving rise to hypothesis and mechanisms, I missed the one on calcium in prostate cancer. Do you have one there?

Dr. Rock: The evidence for a mechanism is weak. The milk connection is not so much driven by milk but that calcium is a marker of milk intake. The major mechanism proposed is that calcium downregulates the synthesis of 1,25-hydroxyvitamin D, but a relationship between this metabolite and prostate cancer risk has not been observed. With regard to colon cancer, I think there is a more biologically feasible mechanistic explanation. I think the discussions also need to note that milk is consumed in developed countries, and that's where they are getting vitamin D, and maybe overconsumption promotes the effect on the insulin-like growth factor.

Dr. Prentice: It is also linked to the high 1,25-dihydroxy vitamin D associated with a low calcium intake, and that's regarded as protective, but as a mechanism it is fairly lean, as you say. I was interested that amongst the plausible mechanisms for the colorectal cancer association you were not including the formation of fecal soaps by calcium. Has the hypothesis that calcium reduces fat absorption now been knocked on the head? I would be interested in hearing where the evidence has gone to on that now.

Dr. Rock: There have been at least a few short-term studies in which people were fed calcium and/or dietary fiber, and/or β-carotene, and samples were examined to identify effects in the lumen. Short-term effects on secondary bile acids were observed, but in the long-term there was no effect on colorectal adenoma recurrence. And that's also true with proliferation, in those reviews from clinical studies it would be wonderful if we had some good markers of proliferation in tissue, but they are too highly variable, and in a lot of those short-term studies, changing these dietary factors did not change the proliferation differentiation or epitosis of colonic epithelial cells.

Dr. Mouane: Several studies show that breastfeeding protects against cancers, particularly ovarian cancer and breast cancer. What do you think?

Dr. Rock: With breast cancer, there have been some studies suggesting that breastfeeding may be helpful, but it's not consistent and it presumably would be because of the effects on estrogen. When a woman breastfeeds, she is not going back into the usual ovulatory cycle that has spikes of estrogen. So there is theoretically an argument. I think the data are there because there are so many studies examining the link between breastfeeding and osteoporosis. Once you have those cohorts identified, it shouldn't be that difficult to find out their breast cancer risk, but the bone scientists aren't always in the same room as the cancer scientists unlike this meeting, where we are. So, maybe we need more meetings like this that focus on foods rather than on simple biological systems.

Reference
