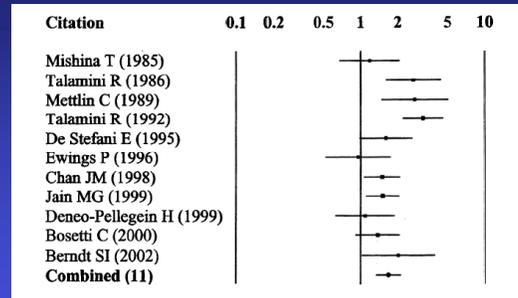


Dairy and Calcium Intake and Prostate Cancer Risk: A Review of Epidemiologic Evidence

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Meta-Analysis Schematic of the OR of Prostate Cancer Associated with Milk Consumption in Case-Control Studies



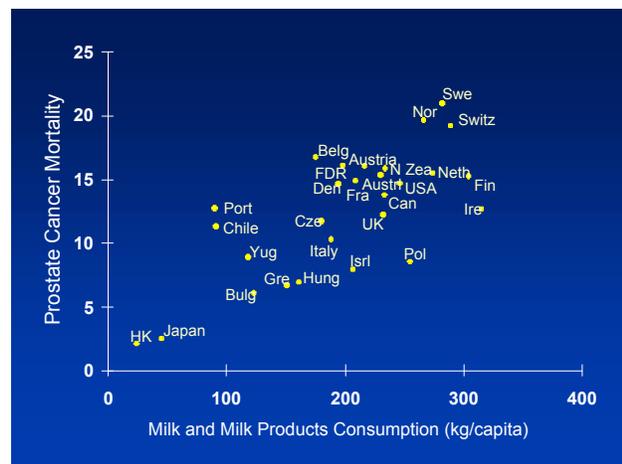
Qin et al., Nutr Cancer 2004

I'm going to talk, very briefly, about the epidemiologic evidence regarding calcium, dairy products and prostate cancer.

Epidemiologic Evidence

- Ecologic Studies
- Case-Control Studies
- Prospective Cohort Studies
- Intervention Study

As you can see, I'm going to talk about the ecologic, case control, and prospective studies, and one intervention study. I won't belabor the ecologic studies. I think Walt (Willett) already discounted them in terms of inferring causality. But it is interesting that milk and milk products have the strongest associations among various food components in terms of risk of cancer mortality. Now, these studies obviously do not prove by any means that milk is important, but these initial studies did suggest the hypothesis that something in our Western diet is important. Could it be milk?



Well, first the case control studies assessed this, and a lot of case control studies were done in the past before there were cohort data available. You can see the dates here of the case control studies, beginning around 1985. And Walt also discounted the case control studies, but I'll show this meta-analysis anyway. This actually is interesting because milk is actually one of the few consistent findings from case control studies with risk of prostate cancer. You can see most of the studies suggest an increased risk. There are about 3 out of the 12 studies in this meta-analysis that are pretty null, but most of them are significantly associated with risk. And if you do the pooled analysis, you get a relative risk of 1.68.

Combined OR of Milk Consumption and Prostate Cancer Risk in Different Types of Studies^a

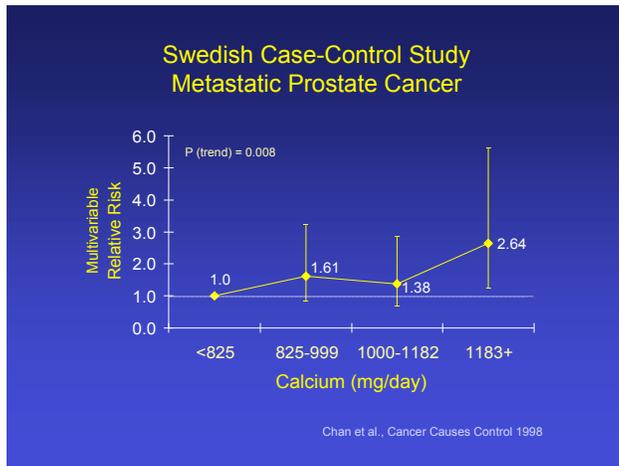
Types of Studies Combined	N	OR ^b	CI
All studies	11	1.68	1.34-2.12
Studies with cases >100	9	1.72	1.32-2.22
Control type			
Population	3	1.46	1.18-1.80
Hospital	8	1.81	1.31-2.57
Milk type			
Milk	6	1.50	1.25-1.80
Milk and dairy products	5	1.61	1.22-2.12
Rate of incidence in country			
<30 / 100,000	4	1.96	1.20-3.20
≥30 / 100,000	7	1.51	1.23-1.86

a. Calculated by a comparison of the highest and lowest categories using Biostat™ software.
b. Value was calculated using a random-effects model.

Qin et al., Nutr Cancer 2004

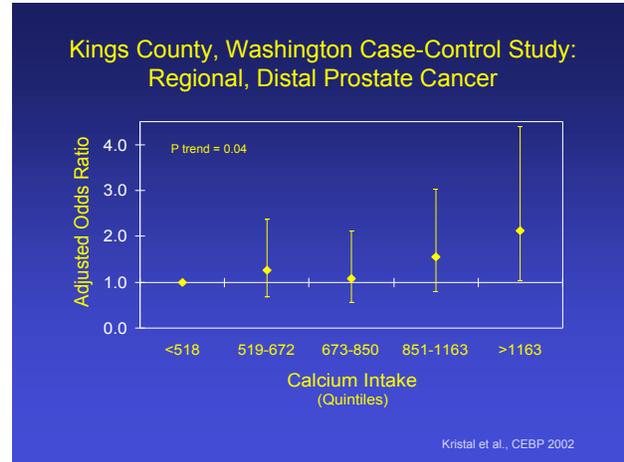
Then in this meta-analysis they looked at a bunch of subgroups based on study size and whether the control types were population or hospital type controls, which is important for epidemiologists. The type of milk, whether it was milk, or milk and dairy products that were studied, and the rate of incidence of prostate cancer, whether it is a high incidence country or a low incidence country, were also examined. As you can see, the results are pretty consistent.

Now, I just want to mention briefly two case-control studies.



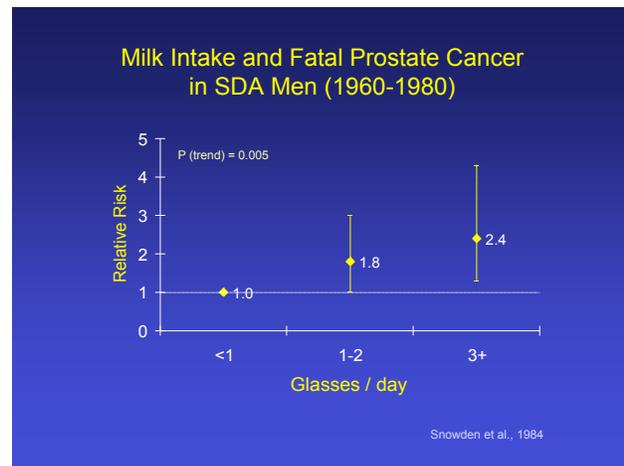
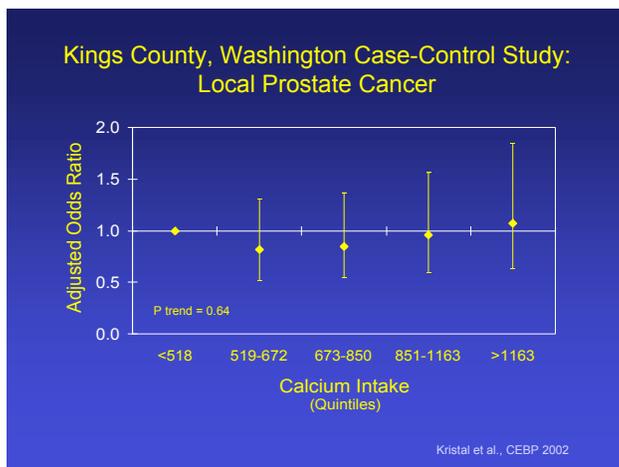
This is Alicja Wolk's study, which was interesting because she was in Boston in 1996-97 and at the time I was looking at data from the Health Professionals' Follow-Up Study, a prospective study. I was focusing on fat and prostate cancer risk because that was a prevalent hypothesis. But I had this kind of weird finding that calcium seemed to be the strongest association. In fact, even when I looked separately at calcium supplements there was an increase in risk. It didn't make any sense to me, and I really didn't know what to do with it. And Alicja, not knowing this, came up to me and said in her case control study she has a strange finding that calcium had a fairly strong association with metastatic prostate cancer. So that actually got me very excited about this potential hypothesis because these are really completely independent data sets and different populations. Also, the point to make here is that the association was stronger with metastatic prostate cancer than with total prostate cancer, and we will see how that's very important.

will really lead to mortality. But, anyway in this study – which we'll see, this becomes a theme -- they looked at calcium intake, including supplements, and found nothing with localized prostate cancers. These are primarily the PSA detected cancers.



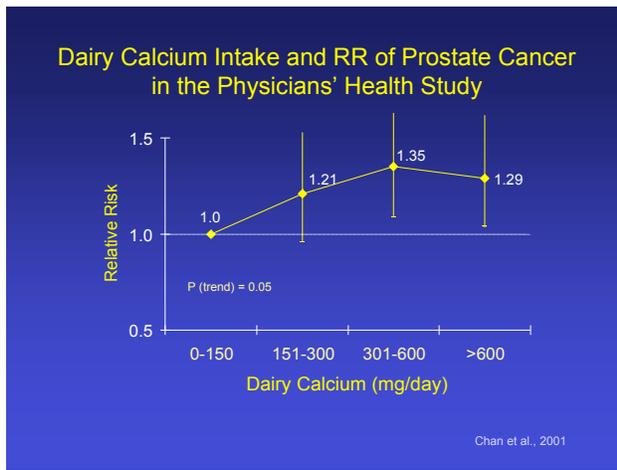
But when they looked at regional or distal prostate cancer, essentially metastatic prostate cancer, there was a significant positive association with about a doubling of the risk. And this interestingly was driven more by calcium or at least in part by calcium supplements. Both the dairy calcium and supplemental calcium had a positive association.

Now we go to the prospective studies. I am going to break this up into two categories, first, the studies conducted in populations without widespread PSA screening, and then the studies in populations with PSA screening.

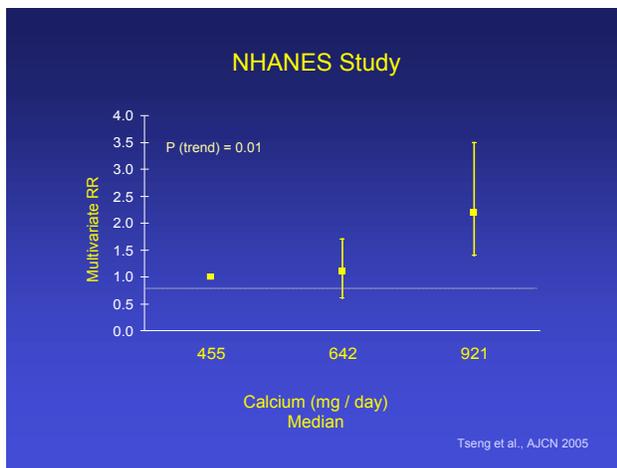


The other case control study I'll mention actually did not make it into the meta-analysis because this was published more recently, right after the meta-analysis. And this was done in what I call the PSA era in the United States. This is a very important issue when we're studying prostate cancer, because PSA, whatever its merits or demerits in regard to clinical evaluation of prostate cancer, really messes up the epidemiology because you detect all of these cancers that are essentially really insignificant, in my mind. They used to be diagnosed at autopsy when 90-year-old men died of something else and never caused them any problems. Now we have all of these cancers, and only about 10 percent of them or so

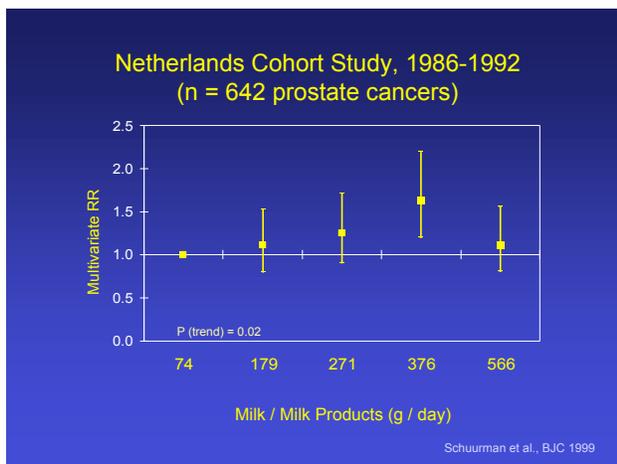
Now, when you look at populations without PSA screening, which is essentially let's say before 1990, I think you see a fairly consistent pattern. These are studies that basically had one dietary assessment and followed men for prostate cancer. And the strong associations seen, for example, in this study – using a very simple questionnaire, they look at glasses of milk per day and fatal prostate cancer -- a relative risk of 2.4 for men having three glasses a day compared to men who rarely drank milk.



The Physicians' Health Study had a relatively simple questionnaire. In fact, we couldn't assess total calcium, we could only assess dairy calcium and there was a significant association. And most of these cases were actually before PSA screening.



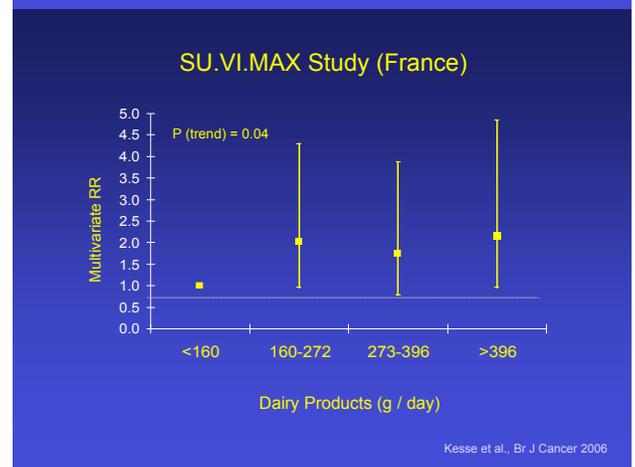
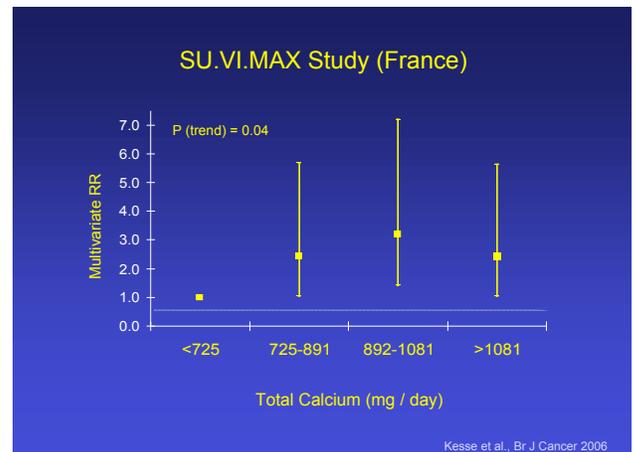
There was another small study based on NHANES (National Health and Nutrition Examination Study) with only about 4,000 men, which is small for epidemiology, and 132 prostate cancer cases. But this study was interesting, again, because it's one of the few pre-PSA studies, and they reported a pretty strong association. They looked at calcium here. They also looked at milk and dairy and there were positive associations, but if you did a multivariate adjustment, it was actually calcium that had the strongest association.



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Now this is the Netherlands cohort looking at milk and milk products. They don't do much screening certainly at this time period in the Netherlands, and their finding was a little equivocal. The trend was significant, you can see the risk goes up, but then in the top quintile it goes down. So this is not strongly supportive.

The ATBC Study (Alpha-Tocopherol, Beta-Carotene Study) was a randomized trial in Finland, and actually became an observational study. The study started in 1985. Initially there was an analysis done by June Chan, looking at 184 cases from 1985 to 1993 - the early follow-up. And there was a slight positive suggestive association, but not significant, which was basically interpreted as a null study. And then recently they reported a lot more cases in an abstract that is now in press. Up to 2002, as the men are aging, there are almost 1,300 cases. And there is not a lot of PSA screening in Finland. So the large increase is due mainly to the aging of the population. And this study had a highly, highly significant association with total calcium with a relative risk of about 1.7. They also saw an association with milk, which is not surprising, and various dairy products. But, actually calcium had by far the strongest association. And if they controlled for calcium and milk or dairy, essentially calcium was what always turned out to be significant. So this will be published soon.



I found this other small study just recently. It also was a randomized trial of vitamin supplements. They had only, I believe, about 80 or 90 prostate cancer cases. This was a study in France, also a population where, even though it's recent, they don't do a lot of PSA screening. And you can see very wide confidence intervals, but they did see a positive trend with total calcium and a very similar association with dairy products. So, essentially these studies, really looking outside the context of PSA screening, are fairly consistent, showing an association with calcium primarily,

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but also with milk, which obviously is the most important source of calcium.

Total Calcium and Prostate Cancer Risk by PSA Test Nutrition Cohort, 1992-1997

Calcium (mg/day)	RR (95% CI)*	
	No PSA before 1992	PSA before 1992
<700	1.0	1.0
700-999	0.9 (0.8-1.1)	0.9 (0.8-1.1)
1000-1499	1.0 (0.8-1.2)	0.9 (0.7-1.2)
1500-1999	1.4 (1.1-1.8)	1.0 (0.7-1.4)
2000+	1.5 (1.1-2.0)	1.0 (0.6-1.6)
	P (trend) < 0.01	P (trend) = 0.93

* Adjusted for age at entry, race, family history of prostate cancer, total energy, total fat intake, education, phosphorus, total vitamin D

Rodriguez et al., CEBP 2003

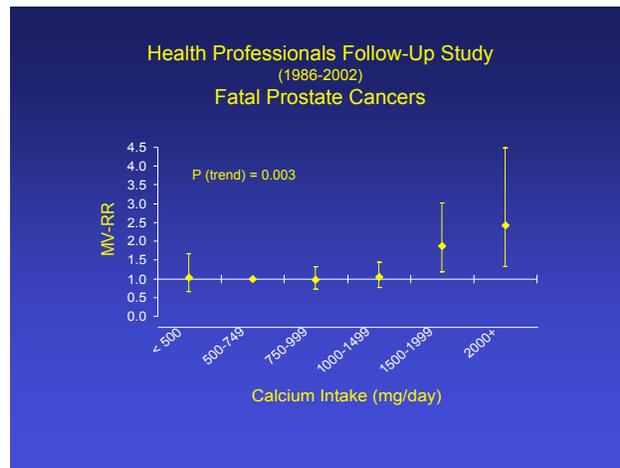
Now if you look at studies conducted during the PSA screening era, there are actually not as many studies. And if you just look at total prostate cancer as the end point, actually the studies are fairly null. But you have to look at them in a little more detail. For example, this was a large cohort study, the American Cancer Society cohort. And you can see the time, 1992 to 1997. This is right at the beginning of widespread PSA screening in the United States. And overall they found a modest, very slight association, not too impressive. But they really only saw something when they looked at men that were really not undergoing extensive PSA screening. So I think that this result is focusing more on the population with cancers that were not PSA detected. If they looked at men who were undergoing PSA screening, they actually saw nothing.

Health Professionals Follow-Up Study

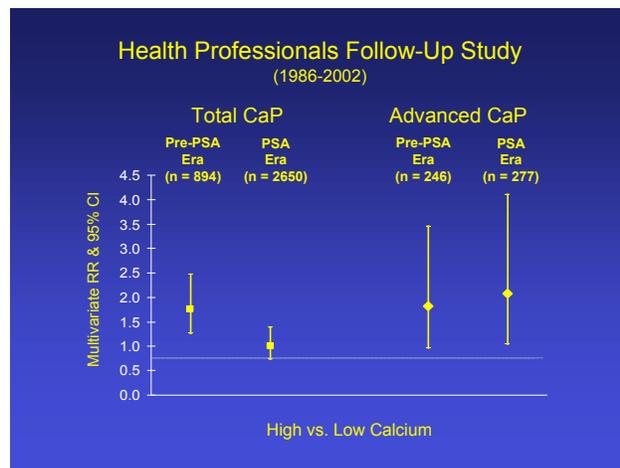
- Published on 1986-1994 follow-up (*Cancer Research*, 1998)
- Updated results on 1986-2002 follow-up
 - 3,544 prostate cancer cases
 - 312 fatal prostate cancers
- Only study with repeated dietary measures

Giovannucci E. et al., Cancer Res 1998
Giovannucci E. et al., CEBP 2005

Now, the Health Professionals' Follow-Up Study is the study that I worked mostly with. We initially published the findings that I described previously, regarding calcium, in 1998, and we did a further follow-up. We now have over 3,500 prostate cancer cases and about 10 percent of them died so far. It's the only study with repeated dietary measures. Now, if we look at total prostate cancer, we actually don't see much.



But if we look at fatal prostate cancer, and remember, these are about 8 or 9 percent of the total, we see a pretty strong association with a relative risk of 2.5 or so in the top category.

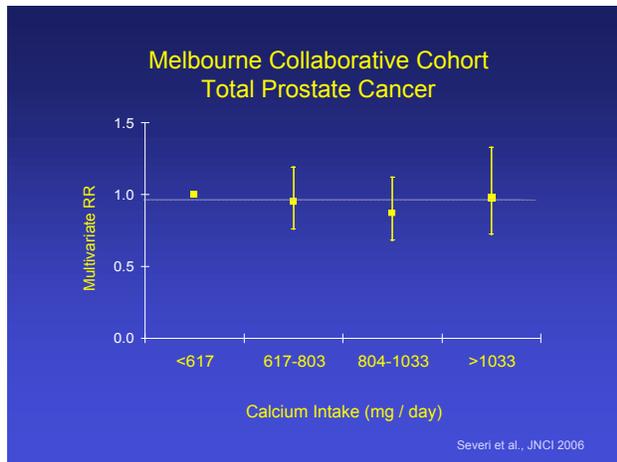


Again, I really want to make this point about PSA screening and what it does to prostate cancer associations. On the left are relative risk and confidence intervals looking at high versus low calcium and total prostate cancer. In the pre-PSA era, if you just look at total prostate cancer, you do see a relative risk of about 1.8, which was significant with about 900 cases. We have tons of cases in the PSA era -- beginning after 1991 is how we define it -- and you see really nothing at all. Interestingly, if you look at the advanced, the metastatic cases in both pre-PSA era and in the PSA era, you see a relative risk of about 2. So it really depends on when you do the study, whether there's PSA screening, and what end point you look at.

Melbourne Collaborative Cohort Study

- 17,049 men 25-75 years old
- Follow-up from 1990-2004
- 674 prostate cancer cases
- 107 aggressive (Gleason >7 or advanced stage)

Severi et al., JNCI 2006



Now this was the study that was mentioned the other day, the Melbourne Collaborative Cohort Study that saw, really, no association. There is PSA screening in Australia. The study is based on a pretty good number of cases, but actually very few aggressive cases. And even the aggressive cases were only based on Gleason score; there were very few that were metastatic. And you really, I think, have to look at metastatic, fatal cases to see something. So this study shows, not surprisingly, that there's no association with total prostate cancer in the PSA screening era.

Intervention Study of Calcium and Prostate Cancer

- Randomized trial of 1200 mg calcium vs. placebo and recurrent colorectal adenoma
- Lower risk of adenoma found (1)
- 672 men followed subsequently for prostate cancer for an average of 10.3 years
- 33 cases in the calcium-treated group
37 cases in the placebo group (2)

(1) Baron et al., NEJM 1999
(2) Baron et al., CEBP 2005

John Baron will talk after me on adenomas. He is the lead investigator of the randomized trial that looked at calcium and recurrent adenomas. Now, they had interesting findings, which he will talk about. But they also went back and looked at prostate

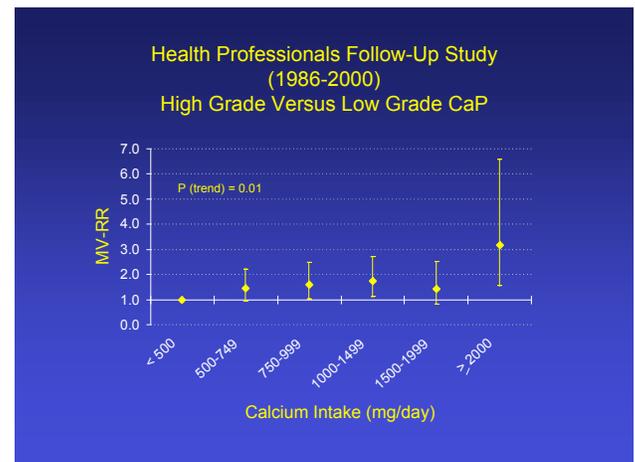
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cancer and saw no association. You see the numbers are pretty small. And the intervention was, I think only about 6 years and it is questionable whether in that timeframe you will see an effect on prostate cancer. But, interestingly, in the earlier follow-up, they actually had, I think, a significant or borderline significant inverse association that sort of got weaker over time.

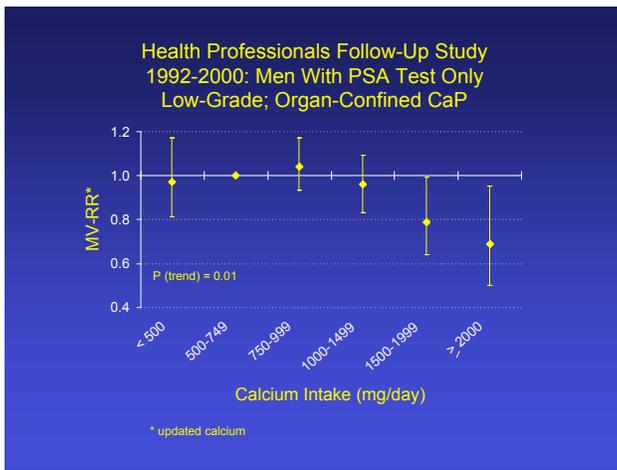
Intervention Study of Calcium and Prostate Cancer

- The finding of no increase and potential benefit is in contrast to epidemiologic studies
- Most of the cancers were likely to be small, moderately well-differentiated, and detected by PSA elevation (mean Gleason score = 6.2)
- Thus, in the Health Professionals Follow-Up Study, we re-examined calcium intake by low-grade and high grade cancers, including those in the PSA era

Now the epidemiologic data that I summarized suggests that it is calcium, but, to be honest, you can't really entirely separate calcium from dairy products, and this study is looking only at calcium. But it was surprising to me that John actually saw this somewhat inverse association. The key point is that most of the cancers were detected probably by PSA screening as the study was done in the 1990s in the United States.



So we went back to the Health Professionals' Follow-Up Study and tried to look at this issue a little more carefully. And so we looked by grade. And as you can see for the high-grade cancers, you see a positive association, a threefold-elevated risk with a high intake of calcium.



- ### Components or Factors of Milk That Potentially Could Influence Prostate Cancer Risk
- Fatty acids
 - Natural / exogenous hormones
 - Increase in IGF-1 level
 - Calcium

When you look at the low-grade, organ confined prostate cancer you actually see an inverse association. So it is almost like prostate cancers are two diseases, the important, high-grade, aggressive prostate cancers that can actually kill you, and the low-grade, PSA detected cancers that probably shouldn't be detected. These are such extremely different findings. You actually have a significant inverse association. Actually, it is almost the identical result that John Baron saw in the trials if you just focus on the PSA detected, early stage cancers. Now you may ask me, are you making this up? How could prostate cancer be two diseases? Well, you know, interestingly, it probably is if you look at other risk factors that people will accept like obesity.

I think Walt summarized components of milk that can potentially increase risk of prostate cancer, so I won't get into that.

- ### Supporting a Role for Calcium
- 3 recent studies found an association with supplemental calcium
 - Typically, calcium intake has been more strongly related to risk than total dairy products

	Calcium	Obesity	5 α Reductase Inhibitor
PSA rise (normal cells)	↓	↓	↓
Non-aggressive prostate cancer	↓	↓	↓
Aggressive prostate cancer	↑	↑	↑

Again, the data seem to point toward calcium, and that's based on three studies. Actually, only three studies had the ability to look at supplemental calcium, and they saw an association with supplemental calcium. And also for almost every study that assessed total calcium and dairy products, the associations were consistently stronger for total calcium than for dairy products.

It seems a little strange that calcium would increase risk. But you actually see exactly the same pattern with obesity, which is associated with lower PSA. There actually was a study recently, The Prostate Cancer Prevention Trial that showed that calcium supplements seem to lower PSA, or at least are associated with a lower rate of increase in PSA over time. So calcium does seem to do something to PSA level that is associated with non-aggressive prostate cancer inversely, and aggressive prostate cancer in a positive sense. And, actually, if you look even at randomized trials with 5 alpha reductase inhibitors, which are blocking dihydrotestosterone, you see the same pattern, a reduction in PSA, very clearly. They actually saw a reduction in low-grade prostate cancer and an increase in high-grade prostate cancer. Now they haven't followed these people to see if those who got 5 alpha reductase inhibitors will die more from prostate cancer, but, clearly, there was a difference between the high-grade and low-grade prostate cancers.

- ### Conclusion:
- Positive associations with milk, calcium are observed primarily for
- Advanced stage cases
 - Fatal cancers
 - Pre-PSA era cases
 - Cases in men without previous PSA screening
 - High grade cancers

The important point that I think I illustrated several times is that when you look at prostate cancer, you have to at least look at some component of the aggressive disease. If you look at epidemiologic

data, there have been associations for various end points, but usually with some component of aggressive disease, whether at advanced stage, fatal, pre-PSA era cases, cases of men without previous PSA screening in the PSA era, or high grade cancers. Also, you can't prove a cause and effect, but the association with calcium and dairy has been seen in multiple situations. And it is possible but unlikely that you would have the same confounding factors in all of these populations.

**Populations showing an increased risk
with calcium and/or dairy intake:**

- United States (diverse)
- Canada
- Uruguay
- Italy
- Sweden
- France
- Finland

sort of messy variable because there are issues with survival. But, for example, in health professionals, most of the fatal cases were cases diagnosed before PSA screening. PSA screening probably has some impact, relatively minimal, on prostate cancer mortality. In the pre-PSA era, there essentially was no good screening test that had any impact on mortality, and despite that, we saw 2.5-fold higher risk in the group with higher calcium intake, which tended to be associated with a healthier lifestyle, going to the doctor more often, for example. So the issue you raise is important but I think it is highly unlikely that screening itself can really explain the findings that we have.

DISCUSSION:

DR. NEVILLE: What might be a mechanism for a relation between high calcium and aggressive cancer? I can't think of one.

DR. GIOVANNUCCI: Well, yes I know but that's like when smoking was first associated with lung cancer, people said, "no way, there can't be an association with smoking, cancer is a genetic disease." The thing that bugged me first about the association is that calcium is tightly regulated in the serum. But there are hormones that regulate calcium. For example, if you have a high calcium intake, parathyroid hormone goes down and calcitonin goes up. Prostate cancers actually do have receptors for parathyroid hormone and for calcitonin. Certainly it's speculative at this point, but we are doing studies to try to look at what mechanisms -- the best that we can do from epidemiology -- potential pathways may be involved. But certainly given the hormonal changes that are associated with either a high or low calcium diet, I think there are plausible mechanisms. If you ask me, which is the mechanism, I can't really tell you.

DR. CAMARGO: I think the hypothesis about the advanced and the localized disease is certainly very tenable, and I support it, but a competing hypothesis relates to what makes people present late in their disease, if you assume the treatment matters and it works for prostate cancer? Could you comment on the steps that you took to address differential presentation, all the factors that relate to why somebody would present with metastatic prostate cancer as opposed to localized, and I think that gets to the PSA issue as well.

DR. GIOVANNUCCI: That's a relevant issue. But, interestingly, if you look at the high calcium group, they actually tended to be more health conscious. They actually had slightly higher rates of PSA screening, which I think is remarkable because if you are getting more PSA screening, if anything, you should have more of a chance of getting an early diagnosis and more localized disease. So despite that, they had higher-grade cancers and were more likely to have metastatic disease at diagnosis. And the other issue, too, is -- fatal prostate cancer is probably the best end point. In epidemiology we're supposed to look at incidence, and fatality is a