Karolinska Institutet

# Dairy Foods and Colorectal and Ovarian Cancer - The good and bad sides of milk

Alicja Wolk, Dr Med Sci
Nutritional Epidemiology
Karolinska Institutet, Stockholm, Sweden

Ed Giovannucci showed the figure of per capita consumption of milk and prostate cancer. If you remember, Sweden was one of the countries with the highest per capita consumption. In our cohort of women, a high percentage, about 30 percent, of total fat comes from dairy, varying between 13 percent and more than 50 percent of fat from dairy foods. Therefore I think it is important to know whether our food frequency questionnaires and other methods accurately measure dairy intake. So we tested whether we can measure the intake of dairy fat by more objective methods.

## Biomarkers of dairy fat intake

Karolinska Institutet

**C 15:0 pentadecanoic acid**

**C 17:0 heptadecanoic acid**

81 women from the Swedish Mammography Cohort (SMC)

- Food frequency questionnaire (FFQ)
- 4 x 1-wk weighed dietary records (3-4 mos apart)
- Adipose tissue (AT)

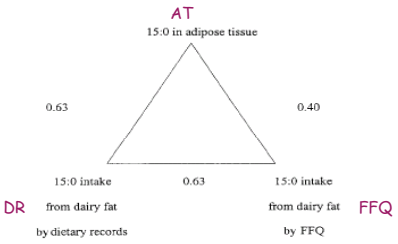
Alicja Wolk October 23-25, 2006 3

Looking for biomarkers, we tested some very special fatty acids in milk fat. One is C:15 or pentadecanoic acid and the other is C:17, heptadecanoic acid. These fatty acids are special in that the human body cannot produce them. So it means that what we can measure in human blood or adipose tissue comes solely from the milk fat we ingest. Adipose tissue is usually the best source of material for the measurement of different fatty acids.

Eighty-one women, randomly chosen from the large Swedish Mammography Cohort, completed food frequency questionnaires. For validation, the same women completed one-week food records. Four times during one year they weighed and recorded everything they ate. From these food records we obtained average consumption of milk and dairy foods and from the same women we had samples of adipose tissue. Before I comment on the correlations, note that the percentage of C:15 in dairy fat is very low, it is 1.05 percent. And for C:17, it is even lower, .061 percent of milk fat. These estimates come from the Department of Dairy Foods and are based on analyses of 73 samples of Swedish milk, collected from 10 different producers from two different regions. So they should be relatively representative for Swedish milk.

## Biomarkers of dairy fat intake

Karolinska Institutet




Wolk A, Vessby B, Ljung H, Barrefors P; Am J Clin Nutr (1998)

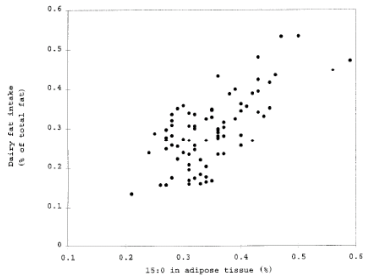
Alicja Wolk October 23-25, 2006 4

We calculated from food frequency questionnaires the intake of C:15 and C:17 and compared these with the fatty acid composition in the womens' adipose tissue. As you can see, the correlation between C:15 in adipose tissue and dietary records was 0.6, relatively high. The correlation between C:15 calculations from dietary records and those from food frequency questionnaires was also 0.6. There was a lower correlation between food frequency questionnaires and adipose tissue, but 0.4 is not bad in nutrition epidemiology. After taking into account the reproducibility of food frequency questionnaires, we could show actually that the correlation with food frequency questionnaires was higher than 0.4. So this means that we can measure the intake of dairy fat by food frequency questionnaires.

## Biomarkers of dairy fat intake

Karolinska Institutet

Scattergram of the untransformed individual data of dairy fat intake and C 15:0 content in the adipose issue




r = 0.63

Wolk A, Vessby B, Ljung H, Barrefors P; Am J Clin Nutr (1998)

Alicja Wolk October 23-25, 2006 5

Here is just the raw data showing that the higher intake of dairy foods is very nicely reflected in our adipose tissue.

There is also much interest in conjugated linoleic acid or CLA, as John Baron just mentioned. So we looked at whether we could quantify CLA. It was not so easy to find a laboratory that could measure CLA in adipose tissue and milk fat because of the very small amounts. CLA, as a percentage of total milk fat in Sweden, was about 0.5 percent and in the adipose tissue it was also about 0.5 percent of total fat. We looked at only one CLA isomer, 9 cis, 11-transoctadecanoic acid because this isomer represents 80 to 90 percent of total CLA in dairy fat. So this is the most important CLA isomer in dairy fat.

## Conjugated linoleic acid (CLA)

9-cis, 11-transoctadecanoic acid - an isomer of CLA

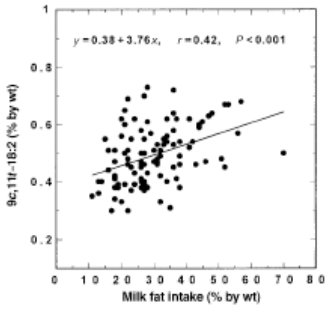
- 123 men (45-79 years old from the source population)
- 2x1-week weighed food records
- 14 x 24-hr recall interviews
- Adipose tissue
- Serum



We did this study in men using two reference methods for intake quantification. One was food records, completed twice during one year, each for one week, and the other was telephone interviews 14 times during one year. So about once per month these men were contacted and interviewed, covering very well the variation during the whole year. We also had adipose tissue and serum samples.



CLA (adipose tissue) and milk fat intake (food records)




r = 0.42

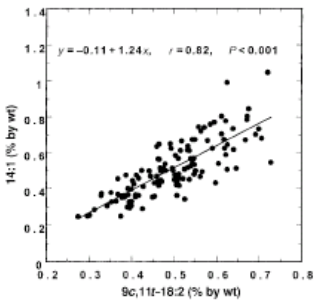
Jian J, Wolk A, Vessy B; Am J Clin Nutr (1999)



The correlation between CLA in adipose tissue and intake based on food records was slightly lower than what we saw for C:15 before, but it was still 0.4, which is okay.



C 14:1 and CLA (adipose tissue)




r = 0.82

Jian J, Wolk A, Vessy B; Am J Clin Nutr (1999)



What is interesting about this figure is you can see that CLA in adipose tissue is extremely highly correlated with C14:1. We couldn't calculate C14:1 from intake because we don't have this value in Swedish food tables. For other countries that have more exact food tables, measuring C14:1 may be an alternative for measuring CLA, although C14:1 is also not present in large amounts. As you can see here, they track each other very closely with a 0.8 correlation. The adipose tissue concentration of this isomer of CLA as well as C14:1 is 0.5 percent in this population of Swedish men. I looked for the composition of fatty acids in adipose tissue in other countries. In Denmark, it was not detectable and no other country has reported the content in adipose tissue. So the question is whether the content is so low that it is too difficult to measure, or whether laboratories are just not able to measure it. Our CLA analysis was done specially by a different laboratory than the one that does our other fatty acid analyses.



Spearman correlations between milk fat intake, C 14:1 and CLA

| | CLA in adipose tissue (*mean 0.5%*) | |
|---|---|---|
| **Milk fat/total fat intake, %** | | |
| *Means 25/82 (CLA 0.16) g/d* | | |
| • 2 x 7 d weighed food records | 0.42 | |
| • 14 x 24-4 recall interviews | | 0.35 |
| **C 14:1 in adipose tissue** | **0.82** | |

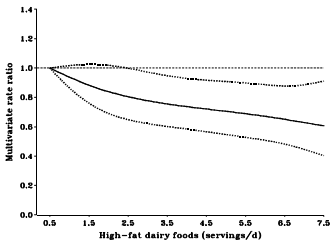
Jian J, Wolk A, Vessy B; Am J Clin Nutr (1999)



These are the correlations from measuring milk fat intake by food records or by telephone interviews. As you can see they were very similar at 0.4 independently for both. So we know now that we can measure CLA.

## High-fat dairy foods and cancer

Colorectal cancer by long-term total high-fat dairy foods consumption
Swedish Mammography Cohort - 60,708 women, 14.8 yrs follow-up, 798 cases




Adjusted for age, BMI, education, energy intake, folate, vitamin B6, cereal fiber, and red meat.
Larsson SC, Bergkvist L, Wolk A; Am J Clin Nutr (2005)



These are updated results, including 800 cases of colorectal cancer, from our Swedish Mammography Cohort data in women during 15 years of follow-up for total intake of high fat dairy foods, including whole milk, whole fat yoghurt, butter and cheese. Unlike the original cohort data, this update is not included in the pooling project because it was done afterwards. I would say the precision is quite high. There is a very nice spline with relatively narrow confidence intervals for this estimate. You can also see from this that consumption of dairy foods is high in Sweden.

## High-fat dairy foods and cancer

Karolinska Institutet

**Colorectal cancer by long-term high-fat specific dairy foods consumption the Swedish Mammography Cohort**

| | | RR (95% CI) | P for trend |
|---|---|---|---|
| Whole milk | Never/seldom | 1.0 | |
| | <1 serving per day | 1.03 (0.82, 1.30) | |
| | ≥1 serving per day | 1.08 (0.90, 1.29) | 0.5 |
| Full-fat cultured mimlk | Never/seldom | 1.0 | |
| | <1 serving per day | 0.87 (0-74, 1.03) | |
| | ≥1 serving per day | 0.81 (0.66, 1.00) | 0.05 |
| Cheese | <1 serving per day | 1.0 | |
| | 1 to <3 serving per day | 0.98 (0.82, 1.16) | |
| | ≥3 servings per day | 0.65 (0.44, 0.96) | 0.04 |
| Butter | Never/seldom | 1.0 | |
| | <15 g per day | 0.88 (0.73, 1.04) | |
| | ≥15 g per day | 0.80 (0.64, 1.00) | 0.03 |

Adjusted for age, BMI, education, energy intake, folate, vitamin B6, cereal fiber, and red meat.

Larsson SC, Bergkvist L, Wolk A; Am J Clin Nutr (2005)



Here we are looking at specific foods. For whole milk we could not see an association, but results for cultured milk (yoghurt) are very close to what John Baron just showed in the meta-analysis done before this study came out. Cheese has the strongest association. At 30 percent fat, regular cheese has high CLA and high calcium. Butter also shows a suggestive association. Although the confidence interval for butter goes up to one, the clear, significant trend indicates that the effect is with some component of the fat because there is no calcium in butter but actually, there is some Vitamin D. I don't know how much.

## High-fat dairy foods and cancer

Karolinska Institutet

**Colorectal cancer by quartiles of conjugated linoleic acid (CLA) --- the Swedish Mammography Cohort (798 cases)**

| | Conjugated linoleic acid intake (mg/d) | | | | |
|---|---|---|---|---|---|
| | <73.4 | 73.4-106.8 | 106.9-149.2 | ?149.3 | *P* for trend |
| Colorectal cancer | | | RR (95% CI)* | | |
| No. of cases | 224 | 219 | 184 | 171 | |
| Colon and rectum | 1.0 | 0.95 (0.8, 1.2) | 0.80 (0.6, 1.0) | 0.71 (0.5, 0.9) | 0.004 |
| Proximal colon | 1.0 | 1.01 (0.7, 1.5) | 0.75 (0.5, 1.1) | 0.82 (0.5, 1.3) | 0.29 |
| Distal colon | 1.0 | 1.03 (0.7, 1.6) | 0.66 (0.4, 1.1) | 0.53 (0.3, 0.9) | 0.01 |
| Rectum | 1.0 | 1.08 (0.8, 1.5) | 1.20 (0.8, 1.7) | 0.75 (0.5, 1.1) | 0.22 |

*Adjusted for age (in mo), body mass index (in kg/m2; <23, 23-24.9, 25-29.9 and ≥30), education (less than high school, high school gradute, or more than high school), total energy intake (continuous), and quintiles of intakes of folate, vitamin B-6, vitamin D, calcium, cereal fiber, and red meat.

Larsson SC, Bergkvist L, Wolk A; Am J Clin Nutr (2005)



So we looked specifically at CLA, and as John just showed you there was a clear inverse association between CLA and colorectal cancer that is slightly stronger for the distal colon, where it is 0.5, with a significant trend. But when we adjust total high fat dairy product intake for CLA, some effect remains, so CLA does not explain all of the effect. This analysis was adjusted for calcium, so what we see is not the effect of calcium, but may be from other milk components that are highly correlated with CLA. So that is the good side of milk, and now we turn to the bad side.

## High-lactose dairy foods and cancer

Karolinska Institutet

**Invasive epithelial ovarian cancer and dairy foods --- the Swedish Mammography Cohort (61,084 women, 13.5 yrs follow-up)**

| | | Serous epithelial tumors, n=125 RR (95% CI) | P for trend | Other epithelial tumors, n= 141 RR (95% CI) | P for trend |
|---|---|---|---|---|---|
| Total milk | Never/seldom | 1.0 | | 1.0 | |
| | ?1 | 1.5 (0.8, 2.9) | | 1.1 (0.7, 1.8) | |
| | (?1/wk)<2 | 2.1 (1.2, 3.7) | | 0.8 (0.5, 1.3) | |
| | ?2 | 2.0 (1.1, 3.7) | 0.04 | 1.0 (0.6, 1.6) | 0.7 |
| Total yogurt | Never/seldom | 1.0 | | 1.0 | |
| | <1 | 1.3 (0.8, 2.0) | | 0.7 (0.5, 1.1) | |
| | (<1/wk) | 1.4 (0.9, 2.2) | 0.11 | 0.9 (0.6, 1.4) | 0.8 |
| Cheese | <1 | 1.0 | | 1.0 | |
| | 1 to <2 | 1.0 (0.7, 1.6) | | 0.9 (0.6, 1.3) | |
| | ?2 | 1.1 (0.7, 1.9) | 0.7 | 1.3 (0.8, 2.1) | 0.2 |

Larsson SC, Bergkvist L, Wolk A; Am J Clin Nutr (2004)



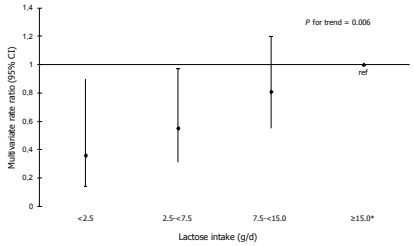
Stephanie Smith-Warner will talk about this in more detail, showing the results of the pooled analysis, but when we compare studies from other countries sometimes the differences might be explained by other factors. So I want to show you that in this Swedish cohort with exactly the same factors, the same women and the same exposures that I have shown for colorectal cancer, we now see the opposite effect, a positive association with ovarian cancer.

## High-lactose dairy foods and cancer

Karolinska Institutet

**Lactose intake and serous epithelial ovarian cancer --- the Swedish Mammography Cohort**

Multivariate rate ratios (RRs) and 95% CIs




Adjusted for age, BMI, education, parity, OC, fruit, vegetables, energy intake.

Larsson SC, Bergkvist L, Wolk A; Am J Clin Nutr (2004)



And this is shown specifically for lactose. In this case we have chosen as a reference the high lactose intake, corresponding to approximately two glasses of milk, with the lowest lactose intake representing about 50 milliliters of milk, about the amount we put in coffee.

## Conclusions

Karolinska Institutet

- C15:0 in adipose tissue is a valid biomarker of dairy fat intake
- CLA (9c 11t – 18:2 isomer) in adipose tissue is also reflecting dairy fat intake
- High-fat dairy foods are associated with decreased risk of colorectal cancer, partly due to CLA (?)
- High-lactose dairy foods are associated with increased risk of serous ovarian cancer