Implications of Total Energy Intake for Epidemiologic Analyses

Chapter 11

Total Energy Intake

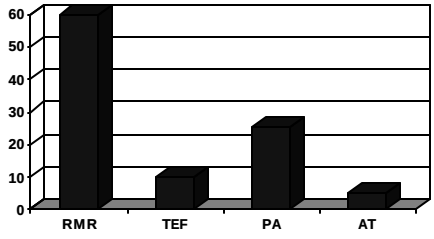
Importance:

- Level of energy intake may important as a primary determinant of disease
- Individual differences in total energy intake may be extraneous, a source of error.
- If energy intake is associated with disease, but not a direct cause, total energy intake may be a confounder

Energy Utilization

energy expenditure =
BMR +
thermogenic effect of food +
physical activity +
adaptive thermogenesis

Figure 11-1: Percent of total energy *expenditure*



Variation in energy *intake* is caused by:

1. Body size
2. Metabolic efficiency
3. Physical activity
4. Weight Change

Often height and weight are used as alternatives to direct measurement of energy intake.

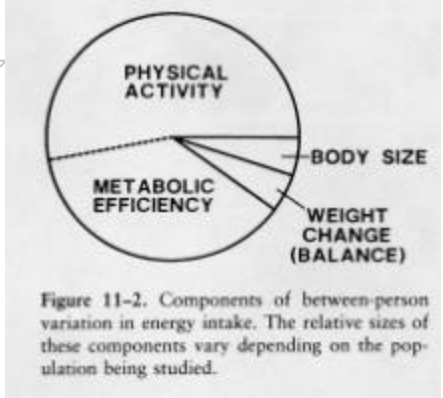
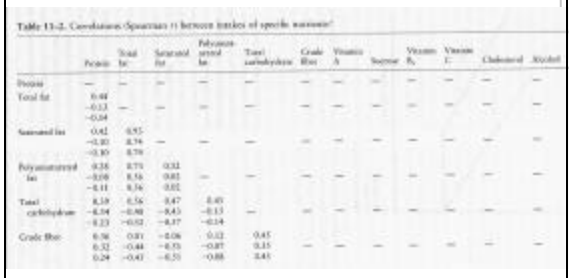


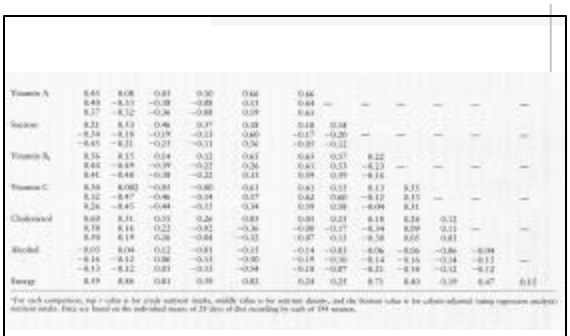
Figure 11-2. Components of between-person variation in energy intake. The relative sizes of these components vary depending on the population being studied.

Total Energy Intake

Intakes of most nutrients are positively correlated with total energy intake (Table 11-2)

Composition of diet may vary by level of total energy intake (Table 11-3)





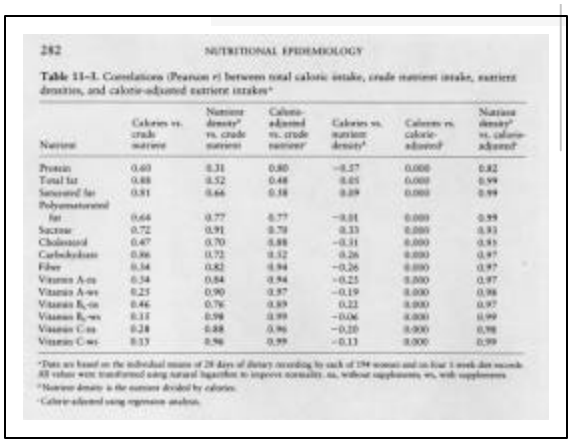


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Table 11–3. Correlations (Pearson r) between total caloric intake, crude nutrient intake, nutrient densities, and calorie-adjusted nutrient intakes[a]

Nutrient	Calories vs. crude nutrient	Nutrient density[b] vs. crude nutrient	Calorie-adjusted vs. crude nutrient[c]	Calories vs. nutrient density[b]	Calories vs. calorie-adjusted[c]	Nutrient density[b] vs. calorie-adjusted[c]
Protein	0.60	0.31	0.00	−0.27	0.000	0.82
Total fat	0.88	0.52	0.48	0.05	0.000	0.99
Saturated fat	0.81	0.66	0.38	0.09	0.000	0.99
Polyunsaturated fat	0.64	0.77	0.77	−0.01	0.000	0.99
Sucrose	0.72	0.91	0.78	0.33	0.000	0.93
Cholesterol	0.47	0.70	0.88	−0.31	0.000	0.93
Carbohydrate	0.86	0.72	0.52	0.26	0.000	0.97
Fiber	0.34	0.82	0.94	−0.26	0.000	0.97
Vitamin A-os	0.34	0.84	0.94	−0.25	0.000	0.97
Vitamin A-ws	0.25	0.90	0.97	−0.19	0.000	0.98
Vitamin B_1-os	0.46	0.76	0.89	0.22	0.000	0.97
Vitamin B_1-ws	0.13	0.98	0.99	−0.04	0.000	0.99
Vitamin C-os	0.28	0.88	0.96	−0.20	0.000	0.98
Vitamin C-ws	0.13	0.96	0.99	−0.13	0.000	0.99

[a]Data are based on the individual means of 28 days of dietary recording by each of 194 women and on four 1-week diet records. All values were transformed using natural logarithm to improve normality. os, without supplements; ws, with supplements.
[b]Nutrient density is the nutrient divided by calories.
[c]Calorie-adjusted using regression analysis.

Adjustment for energy intake:

Can relate disease occurrence to:

1. absolute amount of nutrient (crude)
2. nutrient in relation to total caloric intake
   ? what is biology of nutrient
   ? what is public health consideration
3. nutrient in relation to body size (intake/kg body weight)

Consequences of Not Controlling for caloric intake

If total caloric intake is associated with disease, it may be serious if you fail to account for total energy intake

e.g. Table 11-4 diet and coronary heart,

Crude intake is lower for 11 nutrients, but heart disease cases have lower caloric intake, thus lower nutrient intakes

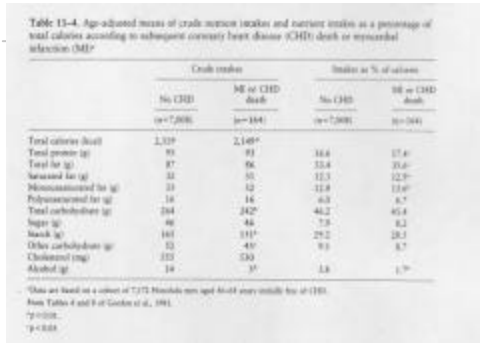


Table 15-4. Age-adjusted means of crude nutrient intakes and nutrient intakes as a percentage of total calories according to subsequent coronary heart disease (CHD) death or myocardial infarction (MI)*

	Crude intakes		Intakes as % of calories	
	No CHD (n=7,808)	MI or CHD death (n=164)	No CHD (n=7,808)	MI or CHD death (n=164)
Total calories (kcal)	2,319	2,149*		
Total protein (g)	93	93	16.6	17.4†
Total fat (g)	87	86	33.4	35.6†
Saturated fat (g)	32	33	12.3	12.9†
Monounsaturated fat (g)	33	32	12.8	13.0†
Polyunsaturated fat (g)	16	14	6.3	5.7
Total carbohydrate (g)	264	242*	46.2	45.4
Sugar (g)	98	86	7.9	8.2
Starch (g)	165	155*	29.2	28.3
Other carbohydrate (g)	52	49†	9.1	8.7
Cholesterol (mg)	355	330		
Alcohol (g)	14	3*	3.8	1.7*

*Data are based on a cohort of 7,972 Honolulu men aged 46–68 years initially free of CHD.
From Tables 4 and 8 of Gordon et al., 1981.
†$p < 0.05$.
*$p < 0.01$.

Variations in caloric intake reflects

- physical activity
- Body size
- metabolic efficiency
- weight change

Fact: any nutrient disease association is not likely to be important in disease etiology if the association is merely a result of differences in caloric intake.

Rule 1: If caloric intake has an important relationship with outcome, then crude nutrient intakes are not instructive.

Rule 2: If caloric excess or deficiency is a primary cause of disease then nutrients that contribute to calories (protein, fat, CHO, alcohol) might be primary exposures and to control for calories might over control.

Correction for caloric intake:

Nutrient densities=nutrient value/
total caloric intake

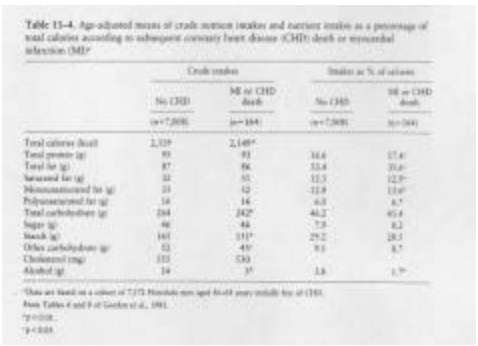
or percent total caloric intake

Problems:

- How to interpret a value that is related both to the nutrient intake and to the inverse of caloric intake.
- As the between person variance of the nutrient diminishes, the nutrient density approaches the inverse of caloric intake.

However:

- If energy intake is NOT related to disease can reduce variation in nutrient intake due to differences in size, physical activity and metabolic efficiency.
- If nutrient and calories are weakly related, can CREATE variation.
- If energy intake IS related to disease can alter direction of relationships (Table 11-4)



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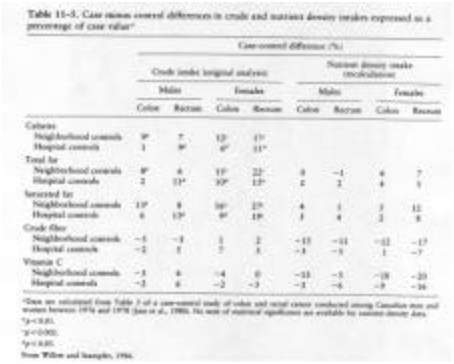
†$p < 0.05$.
*$p < 0.01$.

Example Table 11-5:

- case control investigation of colon cancer.
- cases caloric intake > controls
- cases fat intake > controls
- When look at nutrient densities:

1. fat no association
2. Fiber and vitamin C inverse association



To best study a nutrient and disease relationship:

Ideally we want a measure of nutrient intake that is INDEPENDENT of total calories especially if total calories are associated with disease.

Energy adjusted method:

energy adjusted nutrient intakes are computed as the residuals from the regression model with total caloric intake as the independent variable and absolute nutrient intake as the dependent variable.

Model 1: Disease= b_1 nutrient residual

Note: be sure assumptions for regression are met

Note: if calories are important in relation to the disease then add calories to the model

Model 2: Disease= b_1 nutrient residual+
b_2 calories

Model 3:

Standard multivariate model:

Disease= b_3 calories + b_4 calories

Note: b3 now represents the relationship between calories and disease independent of nutrient

Problem: simultaneous inclusion of strongly correlated variables in the same model

Energy decomposition model:

Model 4:

Disease= b_5 calories from nutrient+
b_6 calories from all other

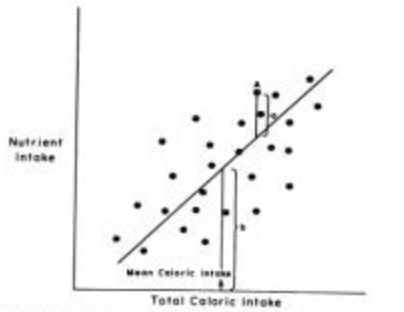
Multivariate nutrient density model:

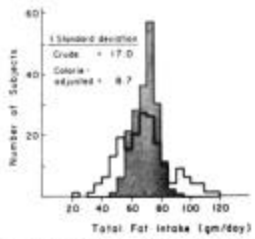
Model 5:

Disease= b_7 nutrient/calories +
b_8 calories

How to present energy adjusted intakes using the residual method (Figure 11-5):

- Energy adjusted nutrient intakes are computed as the residuals from the regression model with total caloric intake as the independent variable and absolute intake as the dependent variable.
- Because residuals have a mean of zero you can add a constant ; logical choice is the predicted nutrient intake for the mean energy intake of the study population or a rounded number of energy intake near the population mean (a+b) where a is the residual value.





Correction for the effects of measurement error

Chapter 12

What is the effect of measurement error on the relationship under study?

- First: What is the type of error?
  - Random (day to day fluctuation) vs. systematic (tendency to deny or exaggerate food intakes or unclear questions)
  - In systematic error repeated measures do not approximate the mean.
- Secondly: What is the level of error?
  - Within person or between persons
  - Between person error random error will average out but the SD will be large
  - Systematic between person error is often the result of a poor measurement tool that omits a commonly eaten food.

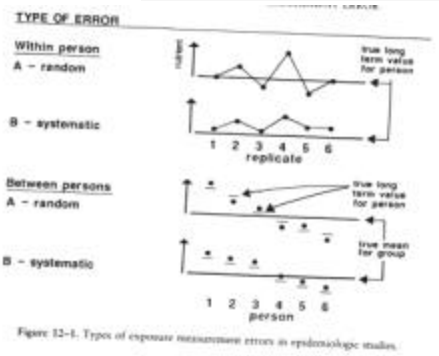


Figure 12–1. Types of exposure measurement errors in epidemiologic studies.

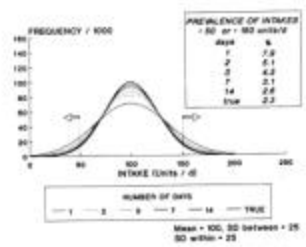


Figure 12–2. Simulation of impact of random error on observed intake distributions. The assumptions are that both between- and within-person variations have a coefficient of variation of 25% (i.e., $s_w^2/s_b^2 = 1$) and that both are normally distributed. Also shown is the impact that days of data collected would have on the proportions of individuals with low (< 50 units) or high (> 150 units) intakes. (From Beaton, 1994; reproduced with permission.)

Correction of Correlation and Regression coefficients, and RR are explained with examples

- A variety of methods exist to correct epidemiologic measures of association for error in the measurement of exposure
- Many of these methods are based on assumptions that should be reviewed (e.g. is the "true measure" really true)

Table 12–3. Observed relative risks for different levels of validity in the measurement of exposure[a]

	True relative risks			
γ[b]	1.5	2.0	3.0	5.0
0.2	1.08	1.15	1.25	1.38
0.3	1.13	1.23	1.39	1.62
0.4	1.18	1.32	1.55	1.90
0.5	1.22	1.41	1.73	2.24
0.6	1.28	1.52	1.93	2.63
0.7	1.33	1.62	2.16	3.09
0.8	1.38	1.74	2.41	3.62
0.9	1.44	1.87	2.69	4.26
1.0	1.50	2.00	3.00	5.00

[a] $RR_o = (RR_t)^\gamma$ where RR_o is the observed relative risk and RR_t is the estimated true relative risk.
[b] The regression coefficient for the true measure on the surrogate measure or (when both measures have the same standard deviation) the correlation coefficient between them.

Issues in Analysis and Presentation of Dietary Data

Chapter 13

Data Cleaning: Blanks and Outliers

- Prior to data collection a decision of what is to be considered acceptable data quality is important
  - For example exclude data from subjects with X number of blank responses (e.g 70/130)
  - What are the allowable ranges for nutrient intakes (e.g. women 500-3500 kcal/day and men 800-4000 kcal/day)

Categorized versus Continuous Presentation of Independent Variables

- Many nutritional variables are categorized in order to present as rate ratios for levels of exposure.
  - Can use quartiles or quintiles
  - Use cut points with *a priori* biological rationale.
  - However there is greater statistical power with the continuous variables

Examination of foods and nutrients

- If a major nutrient is associated with the disease, examine foods to see if there is one major contributor.
- If you look at many foods- should you correct for multiple comparisons? Can you combine into food groups? How do you deal with supplement users? Are there subgroups that are differentially affected?

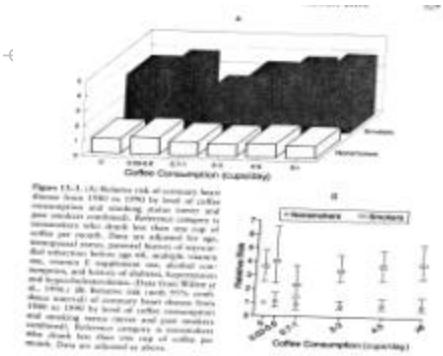


Table 13–2. Choice of approaches for using repeated dietary assessments and related hypotheses

Strategy	Hypothesis
Use earliest measure only	Long latency
Use most recent measure	Short latency
Use consistently high vs. consistently low	Cumulative exposure
Use cumulative average measure	Cumulative exposure
Use change in exposure, controlling for baseline	Relatively short latency

Chapter 16: Dietary Fat and Breast Cancer

Ecologic studies:

mostly due to animal fat r=0.83 vs. vegetable fat r=.18 (fig 16-1)

Potential confounders:

- lean body mass
- obesity
- sedentary lifestyle
- reproductive variables

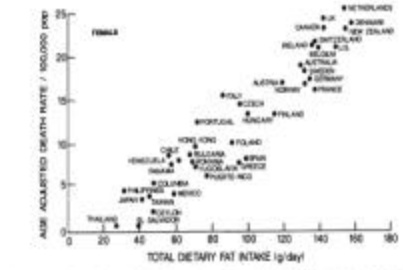


Figure 16-1. Relationship of national per capita fat intake with risk of breast cancer mortality. (From Carroll, 1975; reproduced with permission.)

Migrant studies

migrants from Japan to US: breast cancer rates in offspring are similar to US women.

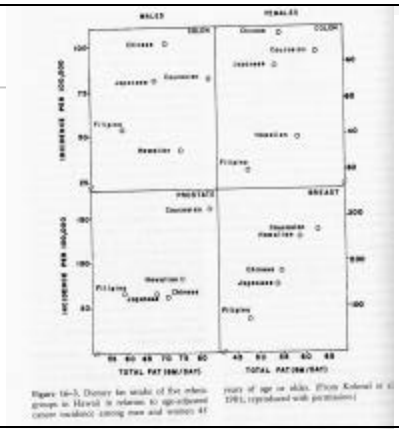
migrants from Italy to Australia and Poland to US immediately attain rates of current homeland.

Special Populations:

lower in Seventh Day Adventists but confounded by SES.

no significant differences between vegetarian nuns and single British Women.

strong correlation between dietary fat intake and breast cancer rates in five ethnic groups in Hawaii (fig 16-3)



Secular trends:

dramatic changes in incidence rates within a country over time indicate that non-genetic factors are important

Iceland(figure 16-4) and Norway (Figure 16-5)

Case Control Studies

- Table 16-1
- Table 16-2
- No evidence of association between fat and breast cancer
- Howe- 12 case-control studies
  - RR=1.35 for 1000 kcal from fat (energy decomposition)
  - RR=1.07 (nutrient density)

Table 16–1. Mean nutrient intake based on 24-hour recall, 4-day diet record, and diet history questionnaire for breast cancer cases and controls, premenopausal and postmenopausal women combined.

Nutrients and series	Dietary method		
	24-hour recall	4-day record	History
Total calories			
Cases	1,697	1,815	1,780
Controls	1,587	1,785	1,730
Difference[a]	109	20	50[c]
(n)[b]	(366)	(309)	(388)
	($p = 0.01$)[c]		
Total fat (g)			
Cases	73.2	81.9	99.1
Controls	69.4	80.0	96.6
Difference	3.7	1.9	2.5
(n)	(386)	(320)	(393)
Saturated fat (g)			
Cases	28.0	32.0	38.3
Controls	26.2	30.5	37.1
Difference	1.8	1.7	1.2
(n)	(383)	(306)	(397)

[a] Mean difference for matched pairs.
[b] Number of pairs.
[c] One-sided p values; other comparisons not statistically significant.
[d] Difference erroneously given as 158 in original table.
Data from Miller et al., 1978.

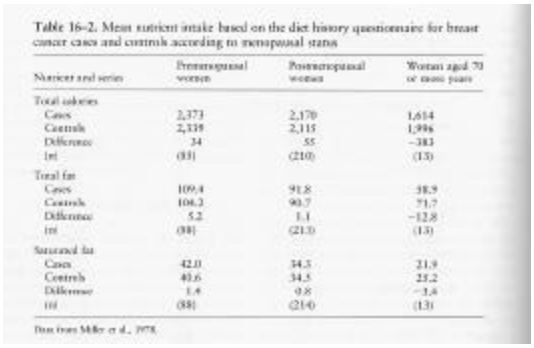


Table 16–2. Mean nutrient intake based on the diet history questionnaire for breast cancer cases and controls according to menopausal status.

Nutrient and series	Premenopausal women	Postmenopausal women	Women aged 70 or more years
Total calories			
Cases	2,373	2,170	1,614
Controls	2,339	2,115	1,996
Difference	34	55	−383
(n)	(93)	(210)	(15)
Total fat			
Cases	109.4	91.8	58.9
Controls	104.2	90.7	71.7
Difference	5.2	1.1	−12.8
(n)	(98)	(213)	(15)
Saturated fat			
Cases	42.0	34.3	21.9
Controls	40.6	34.5	25.2
Difference	1.4	−0.8	−3.4
(n)	(88)	(214)	(13)

Data from Miller et al., 1978.

Cohort Studies

- Largest was Nurses Health Study
  n= 89,538
  aged 34-35 in 1980

FFQ, 4 year follow-up 601 breast cancer cases.

NSD in fat, saturated fat, linoleic acid and cholesterol (Table 16-4).

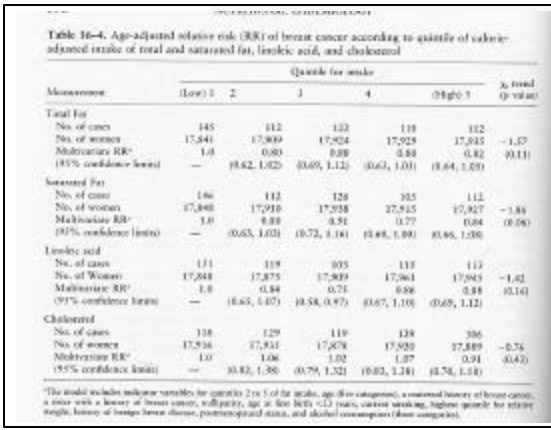


Table 16–4. Age-adjusted relative risk (RR) of breast cancer according to quintile of calorie-adjusted intake of total and saturated fat, linoleic acid, and cholesterol.

Measurement	Quintile for intake					p_t trend (P value)
	(Low) 1	2	3	4	(High) 5	
Total fat						
No. of cases	145	112	122	118	102	
No. of women	17,841	17,909	17,924	17,928	17,935	−1.57
Multivariate RR[a]	1.0	0.80	0.88	0.84	0.82	(0.11)
(95% confidence limits)	—	(0.62, 1.02)	(0.69, 1.12)	(0.63, 1.03)	(0.64, 1.03)	
Saturated fat						
No. of cases	146	112	128	103	112	
No. of women	17,840	17,910	17,938	17,915	17,927	−1.86
Multivariate RR[a]	1.0	0.80	0.91	0.77	0.84	(0.06)
(95% confidence limits)	—	(0.63, 1.03)	(0.72, 1.16)	(0.60, 1.00)	(0.66, 1.08)	
Linoleic acid						
No. of cases	111	119	105	115	113	
No. of Women	17,844	17,875	17,909	17,961	17,943	−1.42
Multivariate RR[a]	1.0	0.84	0.75	0.86	0.88	(0.16)
(95% confidence limits)	—	(0.65, 1.07)	(0.58, 0.97)	(0.67, 1.10)	(0.69, 1.12)	
Cholesterol						
No. of cases	118	129	119	128	106	
No. of women	17,936	17,931	17,878	17,930	17,889	−0.76
Multivariate RR[a]	1.0	1.06	1.02	1.07	0.91	(0.42)
(95% confidence limits)	—	(0.82, 1.38)	(0.79, 1.32)	(0.82, 1.38)	(0.70, 1.18)	

[a] The model includes indicator variables for quintiles 2 to 5 of fat intake, age (five categories), a centered history of breast cancer, a term with a history of breast cancer, nulliparity, age at first birth <25 years, current smoking, highest quintile for relative weight, history of benign breast disease, postmenopausal status, and alcohol consumption (three categories).

Validation Component

- 28 days of diet records for fat intake
- N=173
- Lowest quintile 32% from fat
- Highest quintile 44% from fat
- No data on intake <30%

Comments

- Latent period between exposure and disease of 4 years was insufficient
- Childhood fat intake is important?
- Oldest age at diagnosis 59, need longer follow-up

Prospective Cohort Studies

- Table 16-5;
- n=6 studies
- NSD in breast cancer risk in high vs. low total fat and saturated fat.

Table 16–5. Large prospective studies of total and saturated fat intake and risk of breast cancer

Study	Total no. in cohort	Years of follow-up	No. of cases	RR (95% CI)* (High vs. low category)	
				Total fat	Saturated fat
Nurses' Health Study (Willett et al., 1992)	89,494	8	1,659	0.86 (0.67–1.08)	0.86 (0.73–1.02)
Canadian Study (Howe et al., 1991)	36,837	5	519	1.30 (0.90–1.88)	1.88 (0.73–3.39)
New York State Cohort (Graham et al., 1991)	17,408	7	344	1.00 (0.59–1.70)	1.12 (0.78–1.61)†
Iowa Women's Study (Kushi et al., 1992)	32,080	4	408	1.13 (0.84–1.51)	1.10 (0.85–1.48)
Dutch Health Study (Van den Brandt et al., 1993)	62,573	3	471	1.08 (0.73–1.59)	1.39 (0.94–2.06)
Adventists' Health Study (Mills et al., 1989)	28,341	6	193	—	1.21 (0.81–1.81)

*RR, relative risk; CI, confidence interval.
†Animal fat.

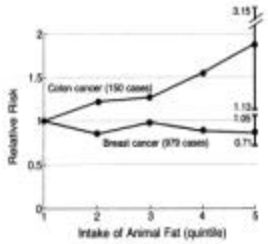


Figure 16-6. Relative risks of colon and breast cancer according to intake of animal fat, adjusted for total energy intake, during 6 years of follow-up. The bars represent 95% confidence intervals for the women in the highest quintile. (From Willett et al., 1990, reproduced with permission. Copyright 1990 Massachusetts Medical Society. All rights reserved.)

Prospective Cohort Studies

- Meta-analysis of these 5 and one additional 1998 study
- N=4980 cases
- N=337,819 women
- No association between breast cancer and intake of total, saturated, mono, polyunsaturated fat (Table 16-6)
- RR=1.02 (0.94 to 1.11)

Table 16–6. Pooled relative risks of breast cancer and 95% confidence intervals for quintiles of energy-adjusted nutrient intake in the pooled analysis of cohort studies*

Nutrient	Quintile 1†	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*p* Value for trend
Total fat	1.00	1.01 (0.89–1.14)	1.12 (1.01–1.23)	1.07 (0.96–1.19)	1.03 (0.94–1.16)	0.21
Saturated fat	1.00	1.01 (0.93–1.14)	1.04 (0.94–1.14)	1.00 (0.90–1.11)	1.07 (0.95–1.20)	0.41
Monounsaturated fat	1.00	1.07 (0.97–1.18)	1.11 (1.01–1.23)	1.10 (0.99–1.22)	1.01 (0.88–1.16)	0.73
Polyunsaturated fat	1.00	1.07 (0.97–1.18)	1.01 (0.94–1.14)	1.06 (0.96–1.16)	1.07 (0.97–1.17)	0.32
Cholesterol	1.00	1.04 (0.94–1.15)	1.02 (0.89–1.16)	1.03 (0.93–1.18)	1.08 (0.97–1.21)	0.19
Energy	1.00	1.01 (0.95–1.11)	1.13 (1.02–1.23)	1.04 (0.92–1.17)	1.11 (0.99–1.23)	0.11

*Relative risks are adjusted for the following variables: age at menarche (<13, 12, 13, 14, or ≥15 years), menopausal status (premenopausal, postmenopausal), parity (0, 1 to 2, >3), age at birth of first child (<20, 21–23, 24–26, 27–29, ≥30 years), body mass index (the weight in kilograms divided by the square of the height in meters) (<23, >23 to <25, >25 to <27, >27 to <29, >29), height (<1.60, 1.60 to <1.64, 1.64 to <1.68, ≥1.68 m), education (<high school graduation, high school graduation, >high school graduation), history of benign breast disease (no, yes), maternal history of breast cancer (no, yes), history of breast cancer in a sister (no, yes), oral contraceptive use ever (no, yes), fiber intake (quintiles), alcohol intake (0, >0 to <1.5, 1.5 to <3, 3 to <10, 15 to <30, ≥ 30 g per day), and energy intake (as a continuous term).
†Quintile 1 values are the reference values.
From Hunter et al., 1996.

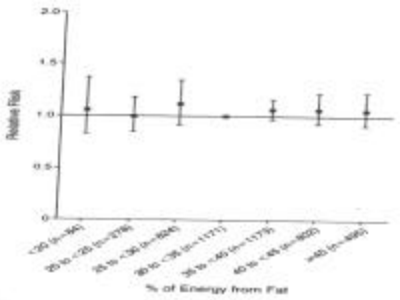


Figure 16–7. Relative risk of breast cancer by percentage of energy from fat in pooled analysis off prospective studies. (From Hunter et al., 1996); reproduced with permission. Copyright 1996 Massachusetts Medical Society. All rights reserved.)

Integration of findings

- Case control studies appear to be influenced by selection bias and recall bias
- Early influence of diet may be important
- Some suggestion that olive oil is protective.
- WHI may answer question with a randomized clinical trial

Why does the large international variation in breast cancer exist?

- Reproductive risk factors
- Selenium and other minerals
- Alcohol
- Specific vegetables
- Phytoestrogens
- HRT/ERT use
- Physical activity
- Height (figure 16-9)