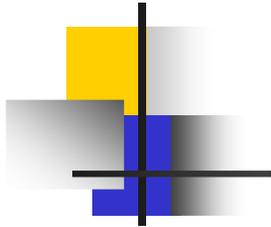


# **The traditional Mediterranean diet and cancer risk**

**Cristina Bosetti**

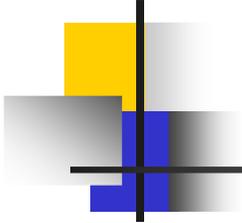
Istituto di Ricerche Farmacologiche "Mario Negri"  
Milan, Italy

ESMO Symposium – Cancer and Nutrition  
20-21 March 2009  
Zurich, Switzerland



## **Ancel Keys** (1904-2004)

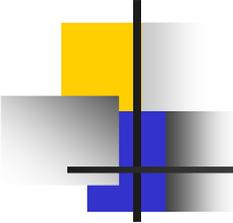




# Traditional Mediterranean diet

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- Abundant and variable plant foods
- High consumption of cereals
- Olive oil as the main added fat
- Low intake of (red) meat
- Moderate consumption of wine



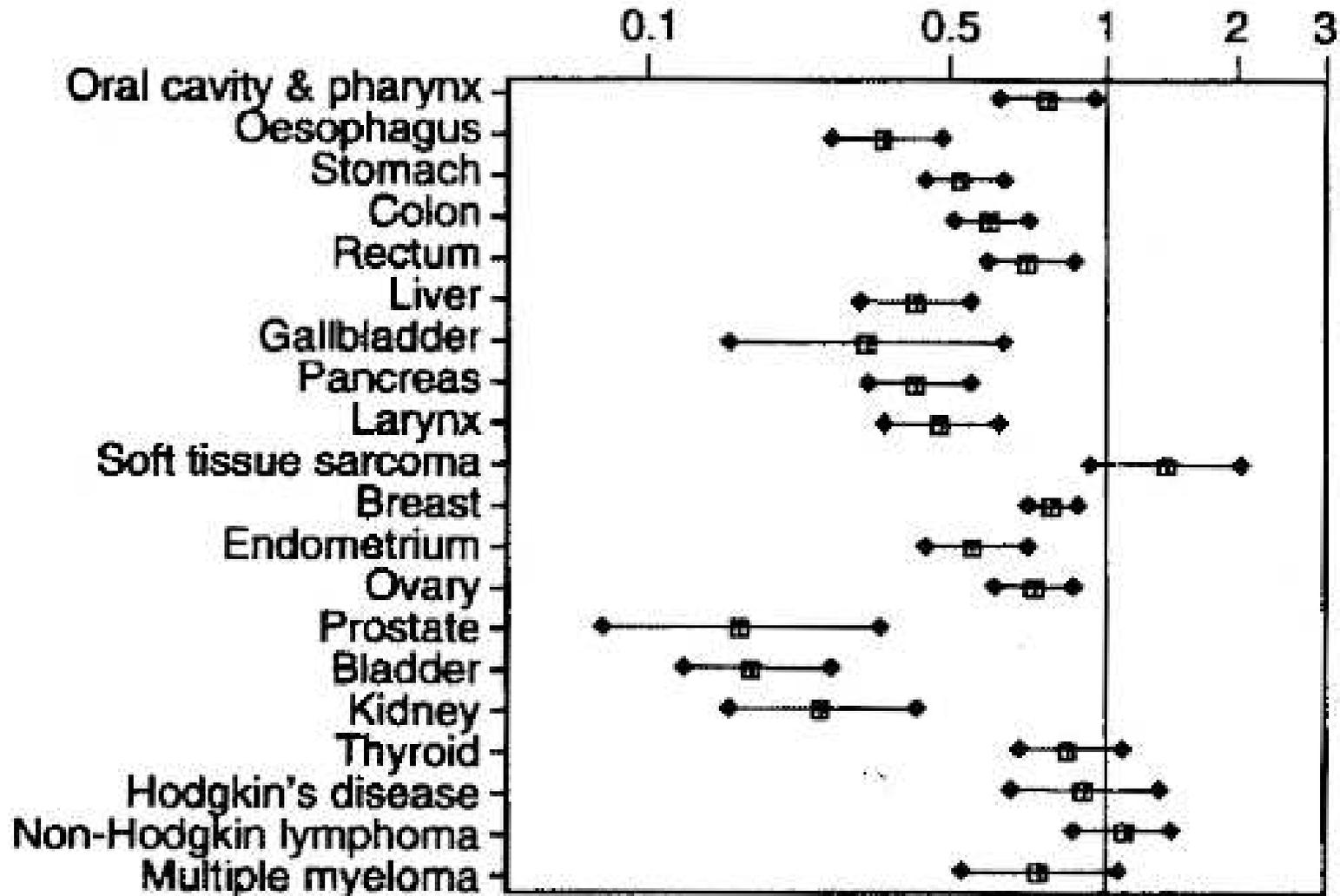
# Fruit and vegetables

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A diet rich in fruit and vegetables protects against common epithelial cancers, including in particular those of the digestive tract.

# VEGETABLES consumption - Relative risks of various cancers. Italian case-control studies

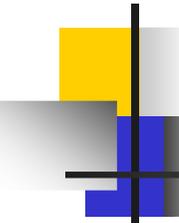


# VEGETABLES and gastric and esophageal cancer. European Prospective Investigation into Cancer and Nutrition (EPIC).

TABLE IV – TOTAL VEGETABLES, TOTAL FRESH FRUIT AND CITRUS INTAKE AND THE RISK OF STOMACH AND OESOPHAGUS ADENOCARCINOMA

Site/type	Cases number	Quartiles <sup>1</sup>			<i>p</i> trend	Calibrated (per 100 g <sup>2</sup> )
		2 HR (C195%)	3 HR (C195%)	4 HR (C195%)		HR (C195%)
<b>Stomach</b>						
Total vegetables	330	1.14 (0.85–1.52)	0.82 (0.58–1.16)	1.15 (0.78–1.70)	0.99	0.91 (0.65–1.28)
Total fresh fruit		1.17 (0.87–1.58)	0.85 (0.61–1.19)	0.99 (0.68–1.42)	0.51	1.04 (0.91–1.20)
Citrus		0.86 (0.64–1.17)	0.67 (0.48–0.93)	0.88 (0.63–1.24)	0.21	0.96 (0.77–1.22)
<b>Cardia</b>						
Total vegetables	94	1.25 (0.68–2.28)	1.53 (0.81–2.89)	1.88 (0.91–3.90)	0.08	0.99 (0.50–1.97)
Total fresh fruit		1.38 (0.81–2.34)	0.72 (0.38–1.37)	0.96 (0.48–1.91)	0.46	1.02 (0.80–1.30)
Citrus		0.72 (0.42–1.23)	0.60 (0.33–1.07)	0.62 (0.32–1.19)	0.08	0.77 (0.47–1.22)
<b>Non-cardia</b>						
Total vegetables	159	1.15 (0.77–1.73)	0.77 (0.47–1.28)	1.12 (0.64–1.97)	0.87	0.96 (0.60–1.52)
Total fresh fruit		0.81 (0.53–1.56)	0.70 (0.44–1.11)	0.85 (0.51–1.42)	0.39	1.03 (0.85–1.26)
Citrus		1.01 (0.65–1.57)	0.73 (0.45–1.18)	1.10 (0.68–1.78)	0.96	1.08 (0.82–1.40)
<b>Intestinal</b>						
Total vegetables	109	1.03 (0.63–1.69)	0.79 (0.44–1.42)	0.89 (0.44–1.79)	0.55	0.66 (0.35–1.22)
Total fresh fruit		0.84 (0.49–1.44)	0.75 (0.42–1.32)	0.86 (0.46–1.61)	0.55	1.02 (0.82–1.28)
Citrus		0.91 (0.53–1.57)	0.67 (0.38–1.19)	0.95 (0.53–1.69)	0.60	1.01 (0.73–1.40)
<b>Diffuse</b>						
Total vegetables	116	1.38 (0.85–2.22)	1.03 (0.57–1.88)	1.40 (0.70–2.81)	0.49	1.18 (0.69–2.03)
Total fresh fruit		1.23 (0.75–2.03)	0.95 (0.55–1.65)	0.68 (0.35–1.31)	0.22	0.97 (0.74–1.29)
Citrus		0.99 (0.60–1.63)	0.58 (0.32–1.04)	0.95 (0.53–1.68)	0.46	0.79 (0.50–1.28)
<b>Oesophagus</b>						
Total vegetables	65	0.88 (0.48–1.63)	0.71 (0.34–1.48)	Tertiles instead of quartiles	0.36	0.72 (0.32–1.64)
Total fresh fruit		0.67 (0.37–1.22)	0.94 (0.49–1.80)	Tertiles instead of quartiles	0.75	0.84 (0.60–1.17)
Citrus		0.56 (0.30–1.03)	0.73 (0.39–1.37)	Tertiles instead of quartiles	0.22	0.77 (0.46–1.28)

(Gonzàles et al., *Int J Cancer* 2006)

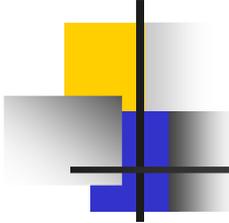


## VEGETABLES and upper aero-digestive tract cancers. EPIC study.

**Table 4** Estimates of relative risk<sup>a</sup> and 95% confidence intervals (CI) for SCC of the upper aero-digestive tract for quintiles of predicted fruits and vegetables intake

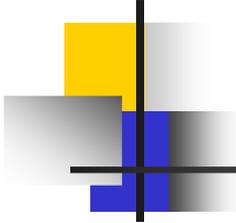
		RR (95% CI)					<i>p</i> for trend
		1. quintile	2. quintile	3. quintile	4. quintile	5. quintile	
Total fruits and vegetables	1	0.64 (0.46–0.89)	0.67 (0.46–0.97)	0.61 (0.40–0.94)	0.60 (0.37–0.99)	0.035	
Total fruits	1	0.63 (0.45–0.88)	0.67 (0.46–0.96)	0.68 (0.46–1.02)	0.60 (0.38–0.97)	0.041	
Citrus fruits	1	0.90 (0.66–1.24)	0.56 (0.38–0.83)	0.84 (0.59–1.19)	0.76 (0.51–1.13)	0.129	
Total vegetables	1	0.92 (0.67–1.27)	1.14 (0.80–1.61)	0.86 (0.56–1.32)	0.80 (0.49–1.31)	0.459	
Fruiting vegetables	1	0.89 (0.65–1.21)	0.90 (0.63–1.28)	0.85 (0.56–1.30)	0.72 (0.42–1.25)	0.249	
Root vegetables	1	0.97 (0.68–1.38)	0.88 (0.61–1.27)	0.67 (0.44–1.01)	0.65 (0.41–1.01)	0.020	
Leafy vegetables	1	0.82 (0.59–1.13)	0.88 (0.61–1.26)	0.83 (0.53–1.31)	0.87 (0.50–1.49)	0.562	
Cabbages	1	1.01 (0.71–1.43)	0.79 (0.53–1.17)	0.71 (0.45–1.11)	0.89 (0.55–1.42)	0.412	
Onion, garlic	1	1.03 (0.70–1.52)	0.98 (0.65–1.47)	0.96 (0.63–1.48)	1.17 (0.73–1.86)	0.447	

(Boeing *et al.*, *Int J CCC* 2006)



# Fruit and vegetables and cancer risk

<b>Evidence for a risk reduction</b>	
<b>Probable</b>	<b>Limited</b>
<i>Vegetables</i> Mouth and pharynx Larynx Esophagus Stomach  <i>Fruit</i> Mouth and pharynx Larynx Esophagus Lung Stomach	<i>Vegetables</i> Nasopharynx Lung Colorectum Ovary Endometrium  <i>Fruit</i> Nasopharynx Pancreas Liver Colorectum
<i>(World Cancer Research Fund, 2007)</i>	



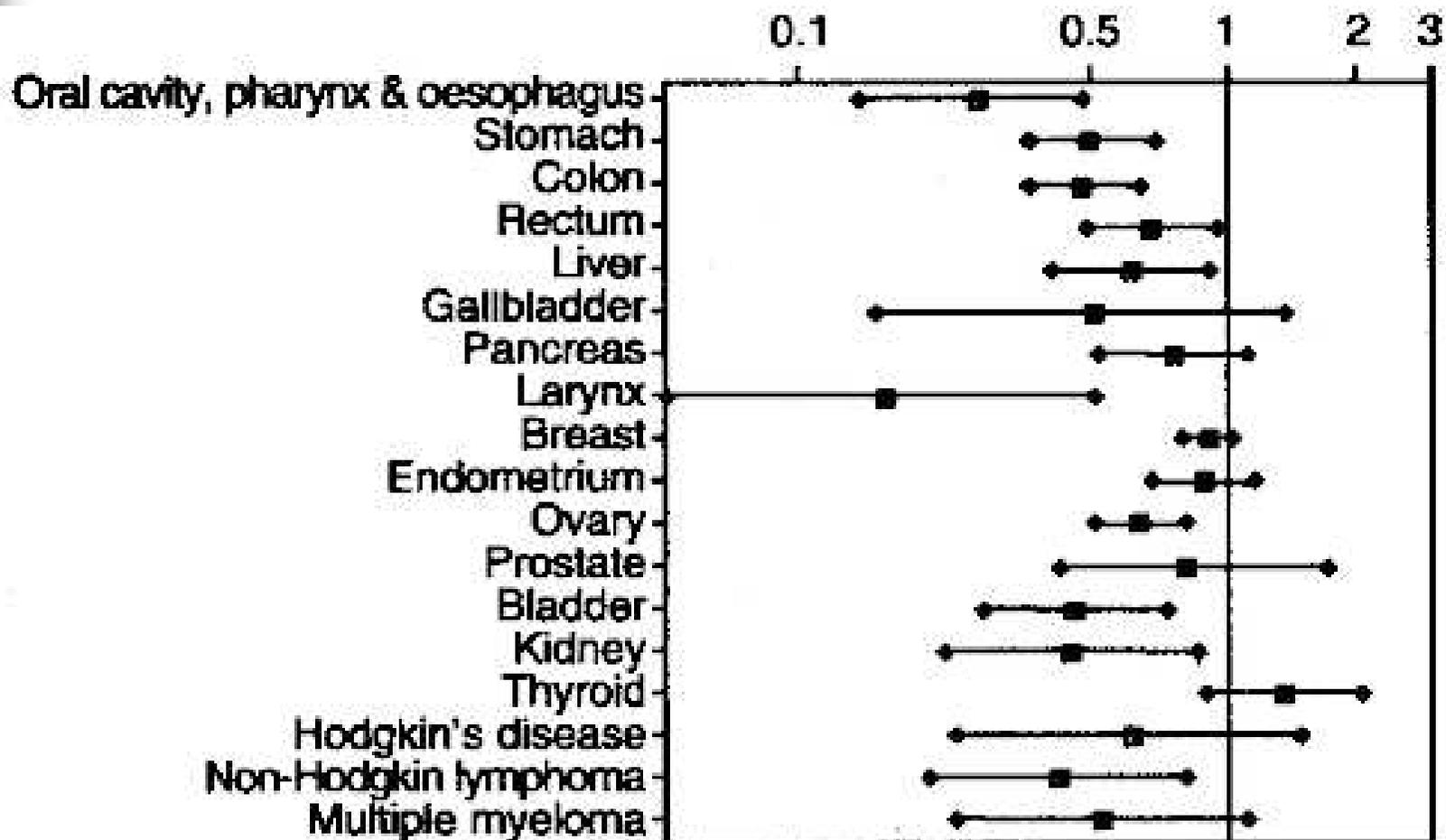
# Whole grains

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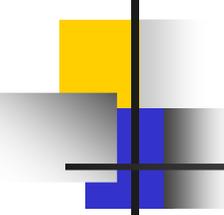


Whole grain food intake has been consistently related to reduced risk of colorectal cancer, but also of several other sites.

WHOLE GRAINS consumption. Relative risks and 95% CI of selected cancers. Italian case-control studies.



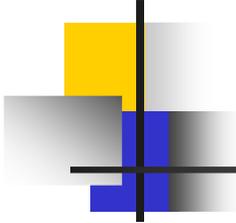
(La Vecchia et al., Proc Nutr Soc 2003)



# Dietary fibres

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Several case-control studies have reported a protective effect of fibres on colon and rectal cancers.



# Dietary fibres – Colorectal cancer

**Relative risk of colorectal cancer according to fibre consumption, among 1953 cases and 4154 controls from Italy.**

Type of fibre	Quintile of intake, OR (95% CI) <sup>a</sup>	
	Men	Women
Cellulose	0.65 (0.55-0.76)	0.66 (0.55-0.79)
Insoluble NCP	0.81 (0.69-0.94)	0.81 (0.67-0.97)
Total insoluble fibre	0.69 (0.59-0.82)	0.69 (0.58-0.82)
Soluble NCP	0.64 (0.52-0.77)	0.66 (0.54-0.82)
Total (Englyst) fibre	0.66 (0.54-0.79)	0.67 (0.55-0.82)
Lignin	0.84 (0.70-1.02)	0.90 (0.72-1.12)

*(Negri et al, CEBP 1998)*

# Dietary fibres – Colorectal cancer

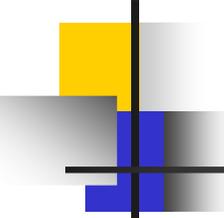
**Relative risk of colorectal cancer according to fibre consumption, among 1065 cases in the EPIC study.**

	Quintile					Hazard ratio (95% CI) for each quintile increase	p
	1	2	3	4	5		
<b>Colorectal cancers</b>							
Number	237	234	200	200	194	..	
Hazard ratio (95% CI)	1.00	0.94 (0.78–1.13)	0.77 (0.63–0.95)	0.76 (0.61–0.95)	0.75 (0.59–0.95)	0.923 (0.873–0.976)	0.005
<b>Colon cancers</b>							
Number	156	158	131	130	131	..	
Hazard ratio (95% CI)	1.00	0.95 (0.75–1.19)	0.75 (0.58–0.96)	0.71 (0.55–0.94)	0.72 (0.54–0.97)	0.908 (0.848–0.972)	0.006
Left colon cancer (n=286)	1.00	0.66 (0.46–0.93)	0.55 (0.37–0.80)	0.51 (0.34–0.77)	0.65 (0.43–0.99)	0.891 (0.804–0.989)	0.030
Right colon cancer (n=287)	1.00	1.21 (0.84–1.71)	0.93 (0.63–1.37)	0.89 (0.59–1.35)	0.73 (0.46–1.19)	0.911 (0.819–1.013)	0.087
<b>Rectal cancers</b>							
Number	81	76	69	70	63	..	
Hazard ratio (95% CI)	1.00	0.92 (0.66–1.27)	0.83 (0.59–1.18)	0.85 (0.59–1.24)	0.80 (0.53–1.22)	0.952 (0.864–1.048)	0.319

Cox's regression using age, weight, height, sex, non-fat energy, energy from fat, and stratified by centre.

Table 3: Numbers of cancers and hazard ratios by quintile of sex-specific total fibre intake

*(Bingham et al, Lancet 2003)*



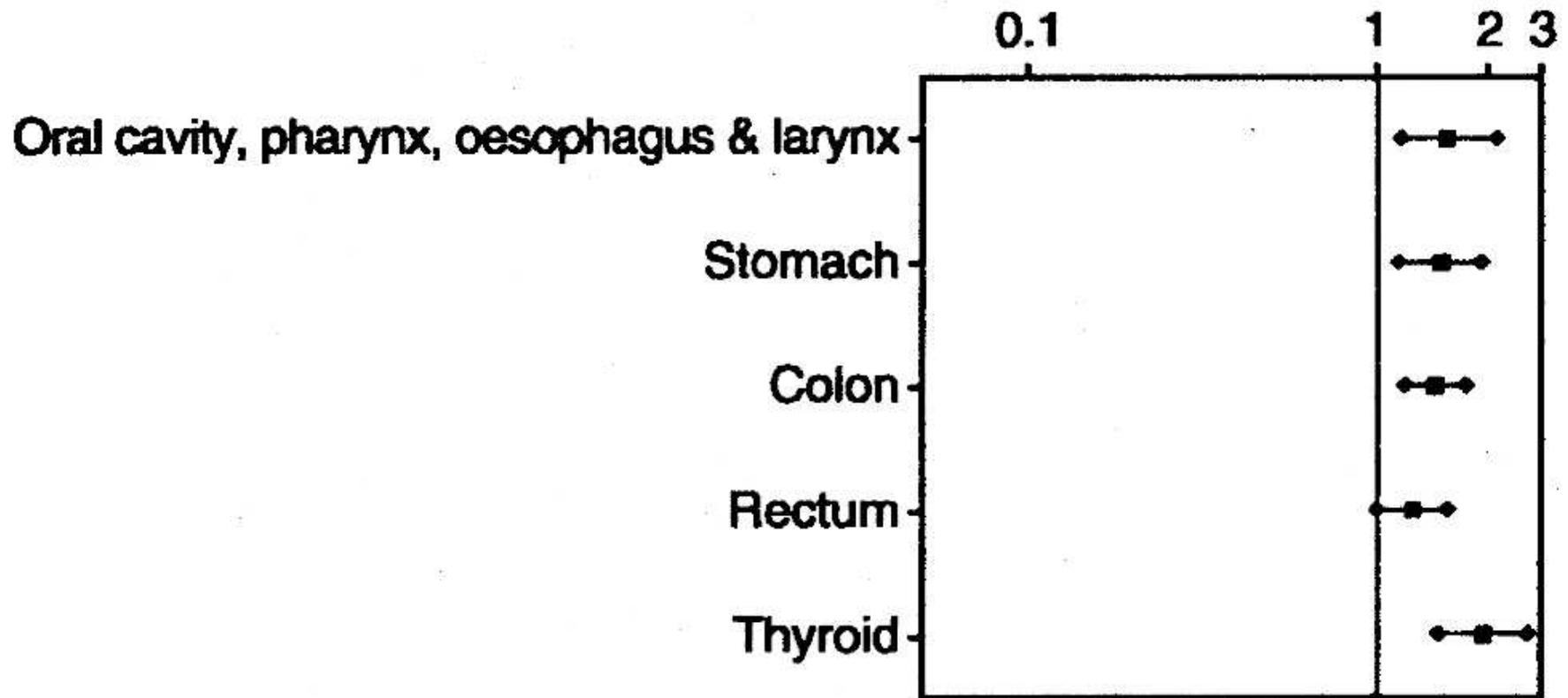
## Refined grains

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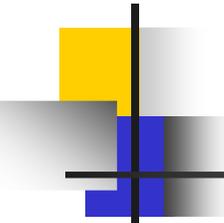


Refined grain intake has been associated to increased risk of stomach, colorectal and upper digestive tract cancers in studies conducted in Mediterranean populations.

REFINED GRAIN consumption. Relative risks and 95% CI of selected cancers. Italy.



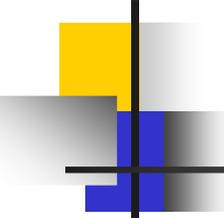
(Chatenoud et al., Am J Clin Nutr 1999)



# Insulin hypothesis

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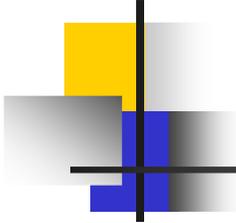
- Refined cereals and sugar can produce
  - glycemic overload
  - insulin resistance
- This may lead to cellular growth promotion *via* specific hormones or insulin-like growth factors



## Glycemic index/load

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The ability to affect blood glucose and insulin levels by dietary carbohydrates is best measured by the glycemic index (GI) and glycemic load (GL), which have been directly associated with risk of several chronic conditions.

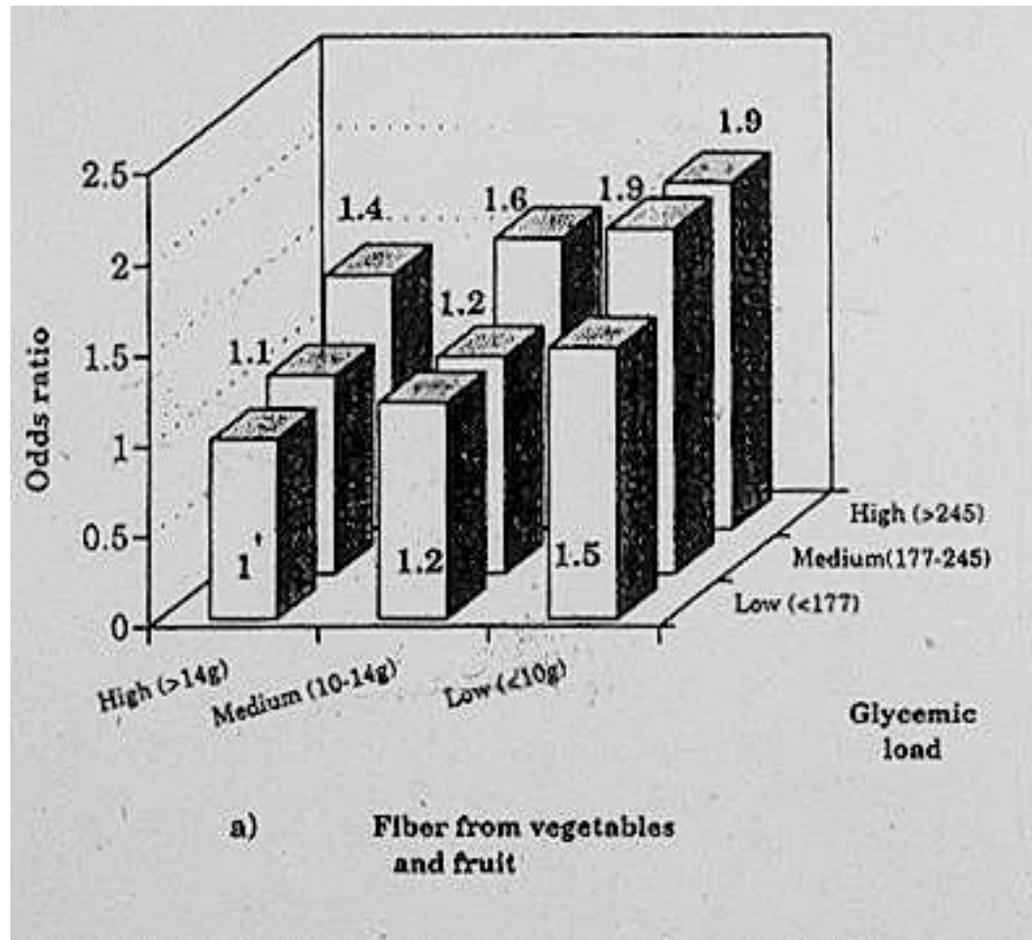


# Glycemic load and gastric cancer

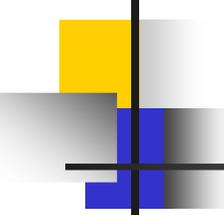
	Cases	Control	OR (95% CI) <sup>a</sup>	OR (95% CI) <sup>b</sup>
<b>Glycemic load</b>				
I	162	551	1	1
II	197	513	1.48 (1.14-1.91)	1.44 (1.11-1.87)
III	192	523	1.66 (1.28-2.17)	1.62 (1.24-2.12)
IV (high)	218	494	2.12 (1.62-2.79)	1.94 (1.47-2.55)
III				
$\chi^2$ trend			29.14 (p<0.001)	21.94 (p<0.001)

(Augustin et al., Ann Oncol 2004)

# Glycemic load and colorectal cancer



(Franceschi et al., Ann Oncol 2001)

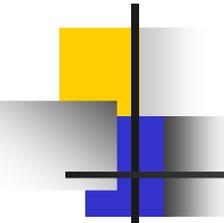


# Fats

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The issue of fats, and of specific types of fats, on the risk of breast and colorectal cancers, as well as of several other neoplasms, remains a major open question.

In a large study from Italy, isocaloric substitution of 5% of total calories as saturated fats by unsaturated ones was associated with reduction in breast (OR= 0.67) and colorectal (OR=0.78) cancer risk



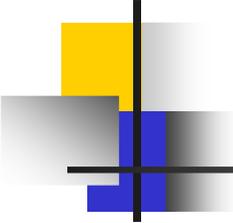
# Olive oil and cancer risk

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Olive oil is a major source of monounsaturated fats in Mediterranean countries, but also an important source of several micronutrients and food components.

It appears to be a favourable indicator of the risk of various common cancers, although the evidence is still open to evaluation.



# Olive oil and breast cancer

**TABLE 2**  
Pooled Odds Ratio and 95% Confidence Interval for the Association between Olive Oil Intake and Breast Cancer

Study	Case/controls	Odds ratio associated with categories of intake					P for trend	b' <sup>a</sup>
		1 (low)	2	3	4	5 (high)		
Toniolo et al. (1989); Italy	250/499	1.0	0.8	1.0	0.8		0.71	-0.0571
Martin-Moreno et al. (1994); Spain	762/988	1.0	0.79 (0.59–1.08)	0.72 (0.51–1.01)	0.66 (0.46–0.97)		0.01	-0.1279
Trichopoulou et al. (1995); Greece	820/1,548	0.97 (0.74–1.27)	1.0	0.75 (0.57–0.98)			—	-0.0860
La Vecchia et al. (1995); Italy	2,569/2,588	1.0	1.05 (0.9–1.3)	0.99 (0.8–1.2)	0.93 (0.7–1.2)	0.87 (0.7–1.1)	0.05	-0.0233

Pooled OR for the highest category of consumption (from the last three studies<sup>b</sup>): 0.79 (0.67–0.92)  
 $\chi^2$  heterogeneity with 2 df: 1.73  
 Weighted average of b' (from all four studies): -0.0581

(Lipworth et al., *Prev Med* 1997)

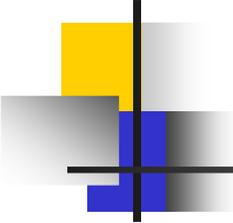
# Olive oil and other cancers

TABLE 3

Studies Evaluating the Association between Olive Oil Intake or Monounsaturated Fat Intake in Olive Oil-Consuming Mediterranean Countries and Cancer of the Colon, Ovary, Endometrium, Pancreas, or Esophagus

Study	Cases controls	Odds ratio associated with categories of intake					P for trend
		1 (low)	2	3	4	5 (high)	
<i>Colorectal cancer</i>							
Benito et al. (1991); <sup>a</sup>	286						
Spain	295	1.00	1.01	0.46	0.72		0.16
<i>Ovarian cancer</i>							
Tzonou et al. (1993); <sup>a</sup>	189						
Greece	200	0.80 (0.65–0.99) per 1 SD increment in intake					
<i>Endometrial cancer</i>							
Tzonou et al. (1996); <sup>a</sup>	145						
Greece	298	0.74 (0.54–1.03) per 1 SD increment in intake					
Levi et al. (1993); <sup>b</sup>	274						
Italy	572	1.0	0.56	0.82			0.05
<i>Pancreatic cancer</i>							
Kalopothaki et al. (1995); <sup>a</sup>	181						
Greece	181 hospital 181 visitor	1.04 (0.86–1.25) per 1 SD increment in intake 0.97 (0.80–1.17) per 1 SD increment in intake					
<i>Esophageal cancer</i>							
Tzonou et al. (1996); <sup>a</sup>	56 ADC <sup>c</sup>	1.00	1.07	1.14	1.23	1.31	0.73
Greece	43 SCC 200	1.00	0.74	0.55	0.41	0.30	0.14

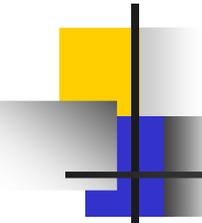
(Lipworth et al., *Prev Med* 1997)



# Olive oil and colorectal cancer

	Tertile of intake, RR (95% CI) <sup>a</sup>		$\chi^2$ trend
	2	3	
<b>Olive oil</b>			
Colorectal	0.87 (0.75-1.01)	0.83 (0.70-0.99)	4.49*
Colon	0.82 (0.68-0.98)	0.81 (0.66-0.99)	4.05*
Rectum	0.96 (0.77-1.19)	0.88 (0.68-1.12)	1.13

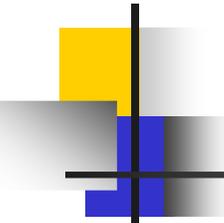
(Braga et al., Cancer 1998)



# Olive oil and upper digestive tract cancers

Cancer	Quintile of intake, RR (95% CI) <sup>a</sup>				$\chi^2$ trend
	2	3	4	5	
<b>Oral/pharyngeal</b>					
Olive oil	0.6 (0.4-0.9)	0.7 (0.5-1.1)	0.7 (0.5-1.1)	0.4 (0.3-0.7)	7.15
Mixed seed oils	0.7 (0.5-1.1)	1.0 (0.7-1.4)	0.9 (0.6-1.3)	1.1 (0.7-1.7)	0.12
Butter	1.2 (0.8-1.8)	1.3 (0.8-1.9)	1.8 (1.2-2.7)	2.3 (1.6-3.5)	22.32
<b>Esophageal</b>					
Olive oil	0.3 (0.2-0.6)	0.3 (0.5-1.2)	0.3 (0.4-1.0)	0.3 (0.3-0.7)	9.98
Mixed seed oils	0.7 (0.4-1.2)	0.8 (0.5-1.3)	0.8 (0.5-1.4)	0.4 (0.2-0.8)	1.41
Butter	1.6 (0.9-2.7)	1.7 (1.0-2.9)	1.5 (0.9-2.6)	2.2 (1.3-3.7)	4.66
<b>Laryngeal</b>					
Olive oil	0.6 (0.4-0.9)	0.8 (0.5-1.2)	0.6 (0.4-1.0)	0.4 (0.3-0.7)	8.62
Mixed seed oils	1.3 (0.8-2.1)	1.8 (1.1-2.9)	2.6 (1.6-4.1)	2.2 (1.3-3.5)	16.16
Butter	1.4 (0.9-2.2)	1.0 (0.6-1.5)	1.4 (0.9-2.1)	0.9 (0.6-1.4)	0.33

(Franceschi et al, 1999; Bosetti et al, 2000; Bosetti et al 2002)

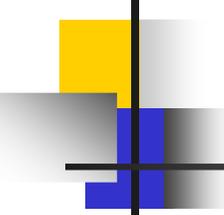


# Olive oil and cancer risk

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Large and multicentric Italian studies showed that olive oil is a favourable indicator of breast, ovarian, colorectal, but mostly of upper digestive and respiratory tract cancers.

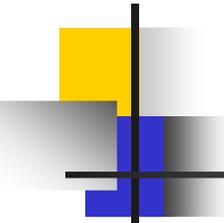


# Olive oil and cancer risk

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In terms of potential biologic mechanisms, it is not clear whether such activity is due to oleic acid itself or to the presence of other antioxidants, such as vitamin E and polyphenols, in olive oil.

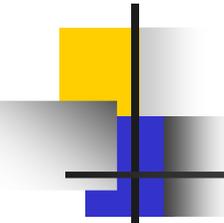
The observed associations may not be due to specific components of olive oil, but to the fact that olive oil indicators of healthier dietary habits



## Mediterranean diet score and cancers of the upper digestive tract

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An *a priori* defined score, summarising eight of the major characteristics of the Mediterranean diet, was applied to data of case-control studies of oral, oesophageal and laryngeal cancers



# Mediterranean diet score and cancers of the upper digestive tract

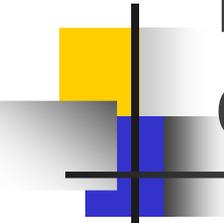
	Cancer, OR <sup>a</sup> (95% CI)		
	Oral/pharyngeal	Oesophageal	Laryngeal
Monounsaturated/saturated fat ratio	0.72 (0.56-0.93)	0.73 (0.51-1.01)	0.97 (0.73-1.28)
Alcohol	4.26 (3.11-5.83)	6.04 (3.79-9.62)	2.77 (2.01-3.83)
Legumes	1.09 (0.87-1.38)	1.03 (0.74-1.42)	0.75 (0.58-0.98)
Cereals	0.77 (0.59-1.00)	0.96 (0.667-1.38)	0.92 (0.68-1.24)
Fruit	1.06 (0.83-1.35)	0.95 (0.68-1.31)	0.82 (0.62-1.07)
Vegetables	0.79 (0.62-1.01)	0.72 (0.51-1.01)	0.51 (0.39-0.67)
Meat and meat products	1.42 (1.11-1.81)	1.50 (1.06-2.13)	1.53 (1.15-2.04)
Milk and dairy products	1.09 (0.86-1.40)	1.24 (0.87-1.75)	1.07 (0.81-1.42)

(Bosetti et al., 2003)

# Mediterranean diet score and cancers of the upper digestive tract

	Mediterranean diet score (number of characteristics)		
	<3	4	≥6
<b>Oral/pharyngeal</b>			
Cases/controls	214/241	120/376	41/201
OR (95% CI)	1	0.41 (0.30-0.57)	0.40 (0.26-0.62)
<b>Oesophageal</b>			
Cases/controls	102/147	66/174	14/83
OR (95% CI)	1	0.63 (0.41-0.95)	0.26 (0.13-0.51)
<b>Laryngeal</b>			
Cases/controls	183/225	98/279	19/124
OR (95% CI)	1	0.47 (0.33-0.66)	0.23 (0.13-0.40)

(Bosetti et al., CEBP 2003)



## Mediterranean diet score and cancers of the upper digestive tract

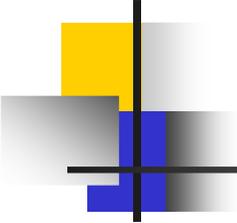
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An *a priori* defined nutritional pattern, which includes several aspects of the Mediterranean diet, favourably affects the risk of cancers of the upper aerodigestive tract

## Conclusions (1)



A low risk diet for cancer would not only imply increasing fruit and vegetables, avoiding red meat, but also prefer whole grain carbohydrates to refined ones, and olive oil and other unsaturated fats to saturated ones.



## CONCLUSIONS (2)

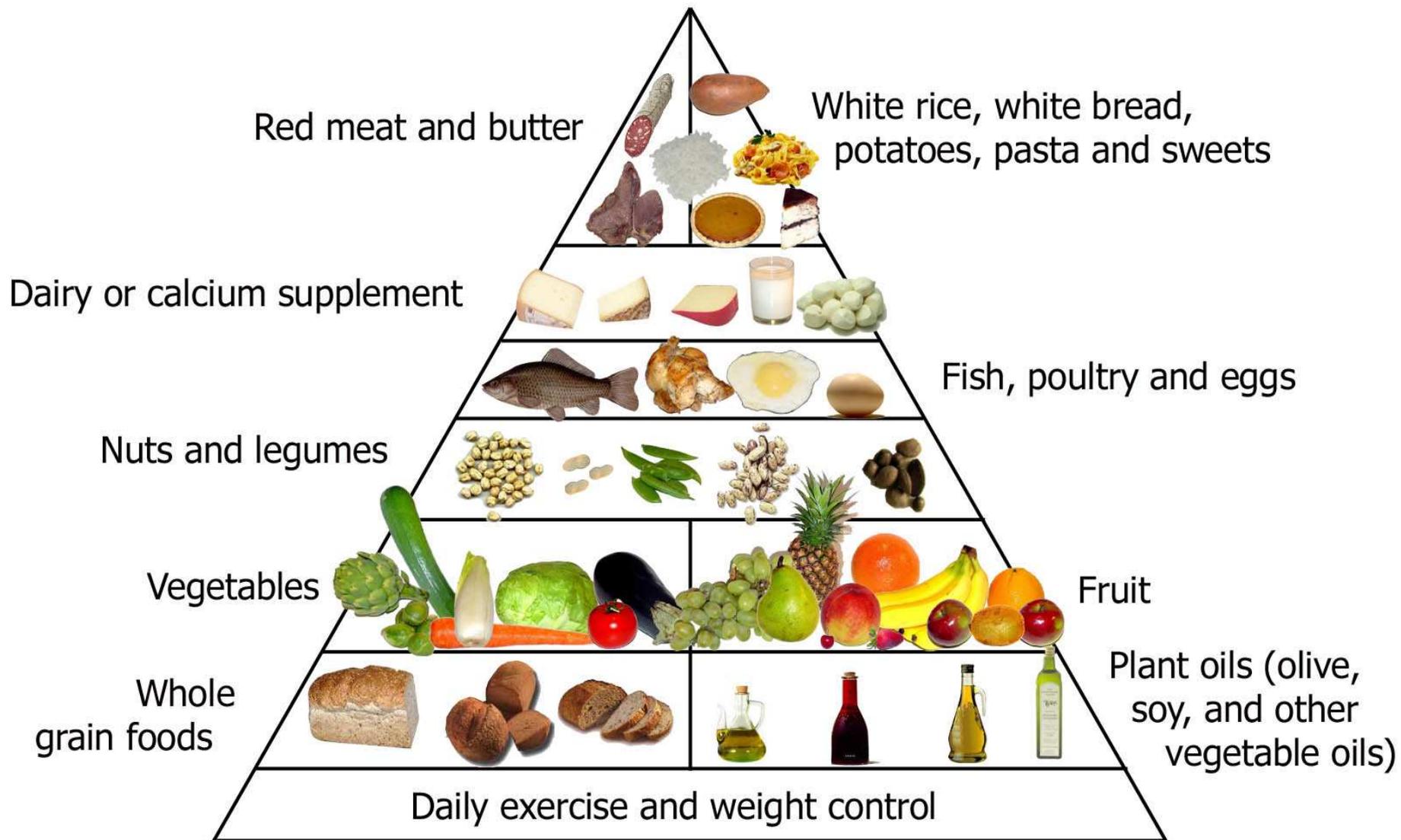
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This also helps control of body weight, which is a priority in cancer prevention



## Mediterranean Diet



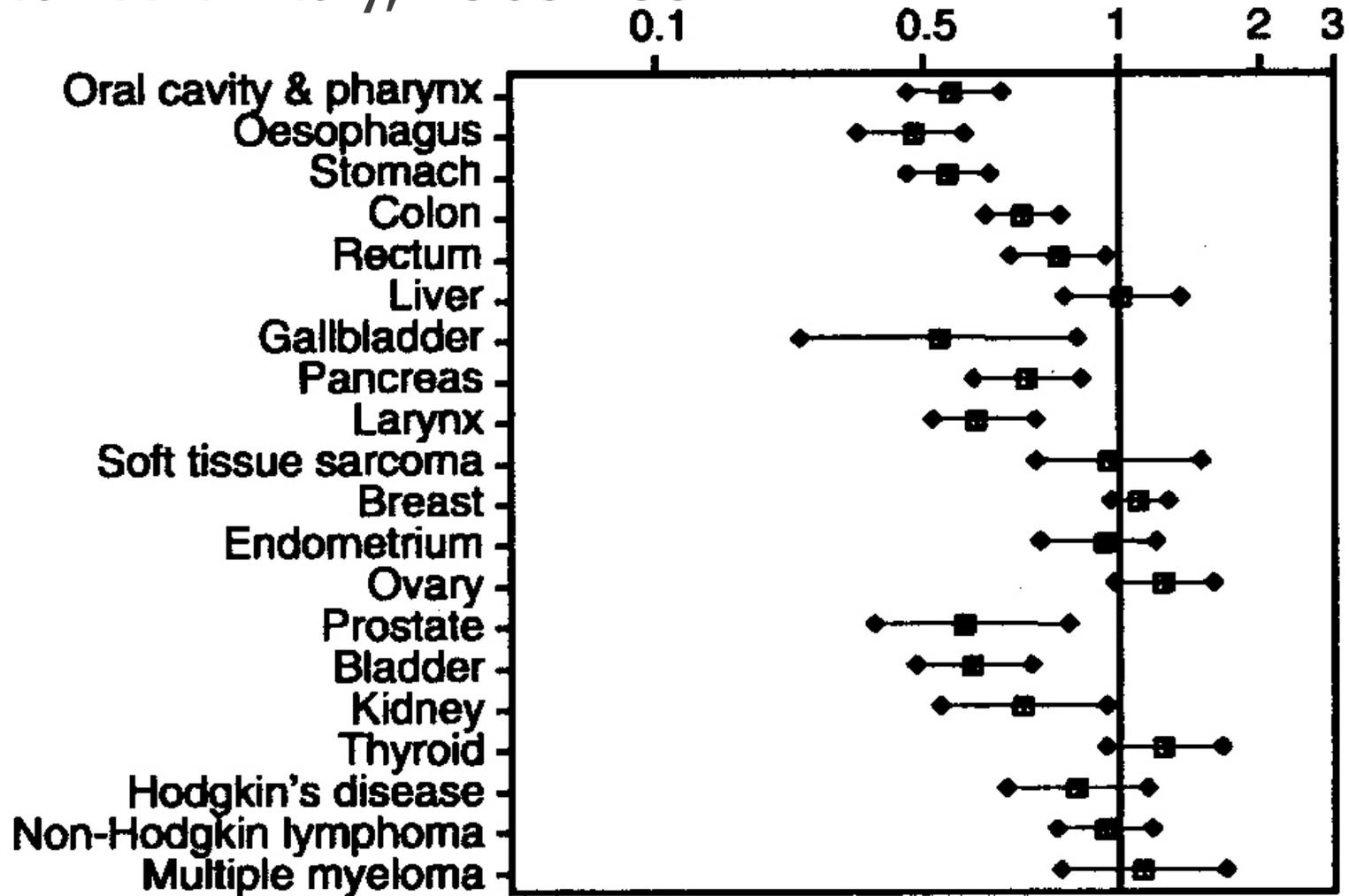


# Fats

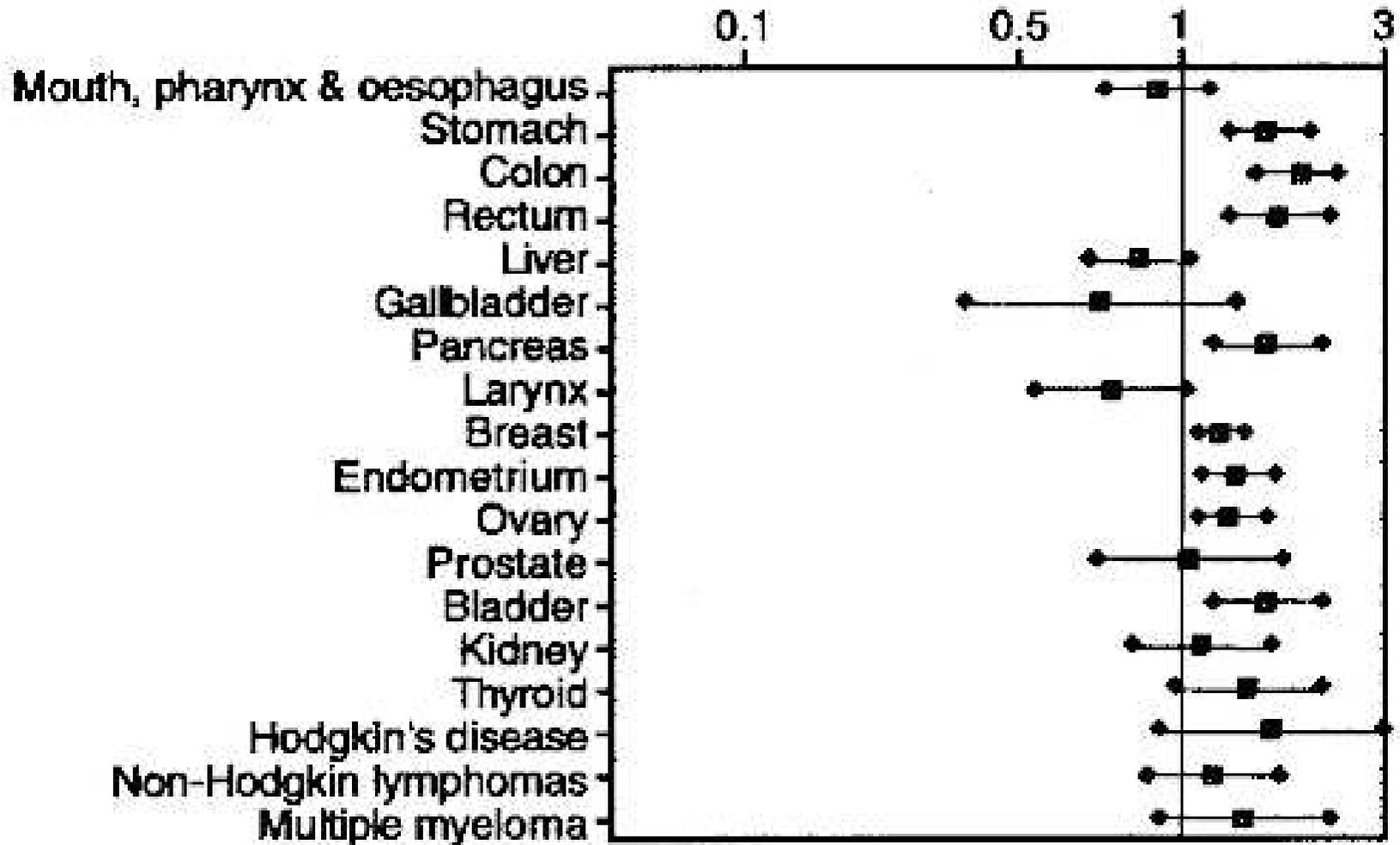
In the EPIC cohort an association between high saturated fat intake and greater breast cancer risk was found (RR 1.13, 95% CI: 1.00, 1.27) for the highest quintile of saturated fat intake compared with the lowest quintile.

*(Sieri et al, Am J Clin Nutr 2008)*

# FRUIT consumption - Relative risk of various cancers. Italy, 1983-1997

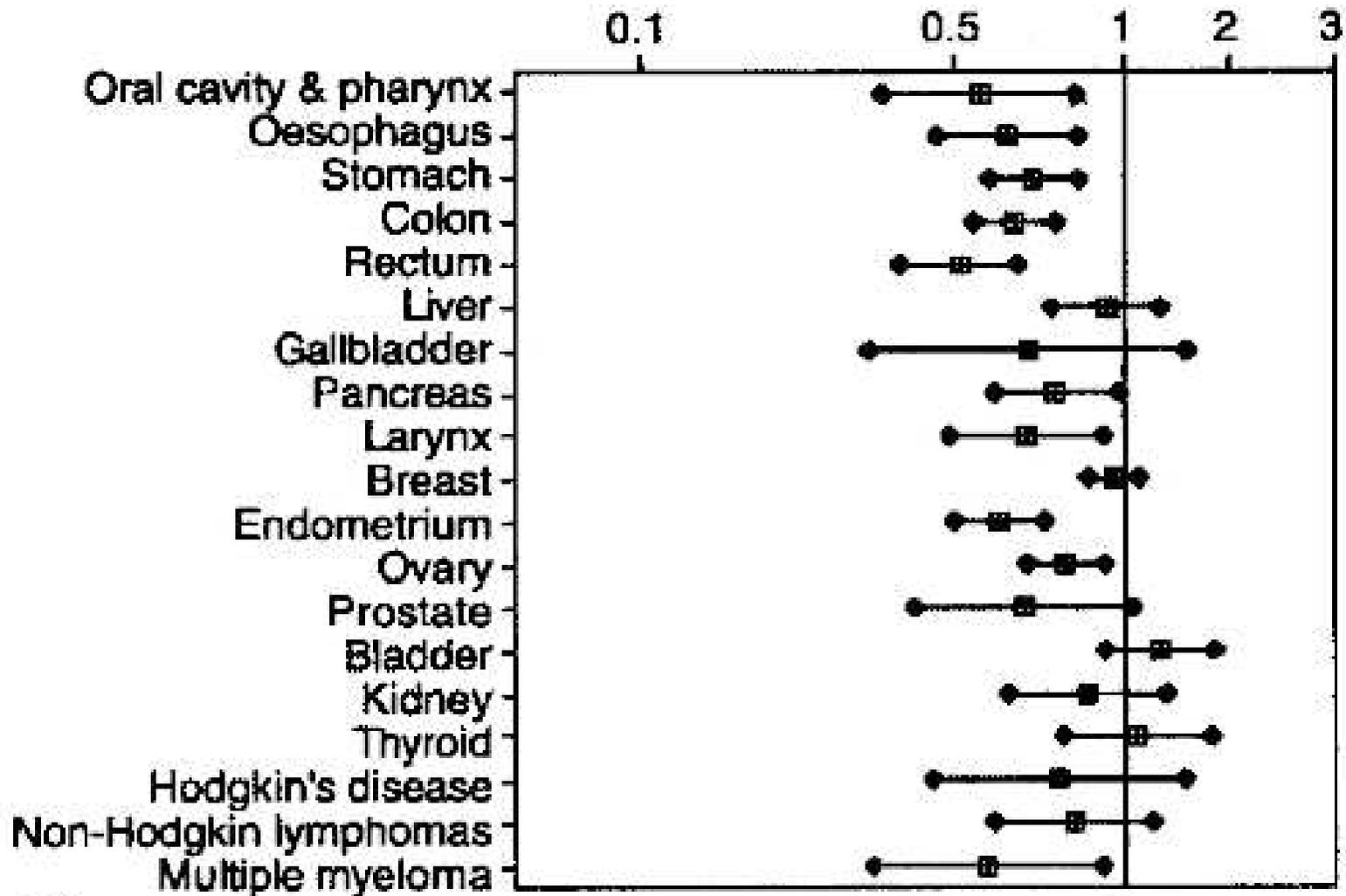


RED MEAT consumption - Relative risk of various cancers.  
Italy, 1983-1997



(Tavani et al., Int J Cancer 2000)

# FISH consumption - Relative risk of various cancers. Italy, 1983-1997



(Fernandez et al., Am J Clin Nutr 1999)