Overweight, diabetes and breast cancer

- *Review of the evidence available to date*
- *Confounding risk factors for breast cancer and diabetes*

Carlo La Vecchia

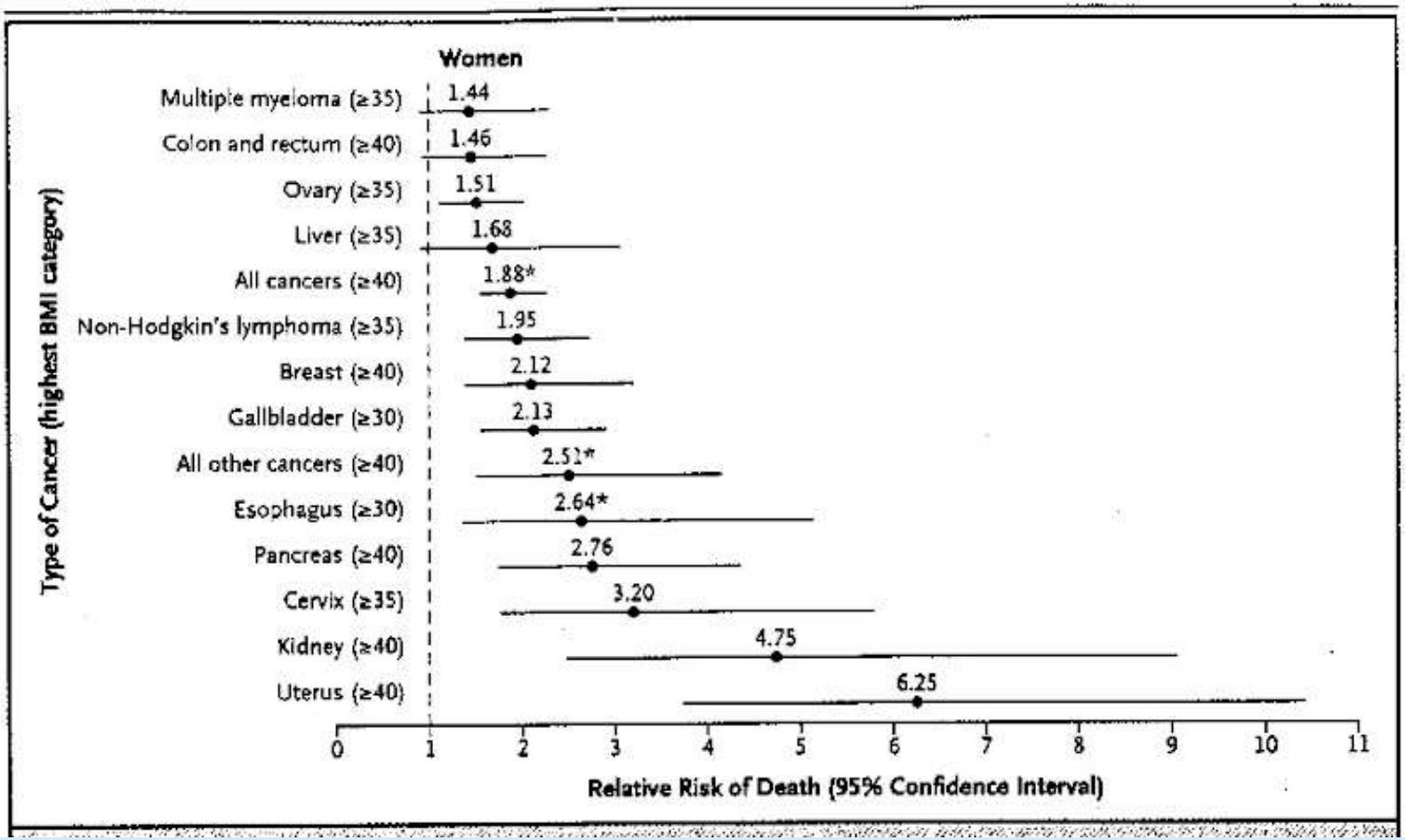
Overweight – ACS–CPS II

Overweight and obesity account for 14% of cancer deaths in US men and 20% in US women

(Calle et al., 2003).

These figures are lower in Italy, i.e. about 3-5%, on account of the lower prevalence of overweight.

Overweight – ACS–CPS II



Calle et al., 2003

Overweight – ACS–CPS II

In the USA, the RR of breast cancer in severe obese women is over 2-fold increased.

Overweight - Endogenous hormones

Breast cancer risk is directly related to overweight and obesity in postmenopause, and this is explained in terms of increased estrogen levels and availability in overweight post menopausal women.

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Overweight - Endogenous hormones

The RR increases with advancing age, reflecting duration of exposure to high estrogen levels.

Overweight – Post-menopausal breast cancer in Italy

BMI	Age (years)					
	50–59		60–69		≥70	
	Cases–controls	OR (95% CI)	Cases–controls	OR (95% CI)	Cases–controls	OR (95% CI)
1 (< 21.8 kg m^{-2})	221:232	1[b]	245:238	1[b]	97:113	1[b]
2 (21.8–23.8 kg m^{-2})	263:219	1.26 (1.0–1.6)	255:189	1.33 (1.0–1.7)	115:109	1.35 (0.9–2.0)
3 (23.9–25.7 kg m^{-2})	267:204	1.34 (1.0–1.8)	255:223	1.17 (0.9–1.5)	97:114	1.05 (0.7–1.6)
4 (25.8–28.4 kg m^{-2})	252:193	1.38 (1.1–1.8)	276:223	1.25 (1.0–1.6)	117:99	1.60 (1.1–2.4)
5 (>28.4 kg m^{-2})	244:204	1.30 (1.0–1.7)	261:215	1.24 (1.0–1.6)	143:89	2.14 (1.4–3.2)

La Vecchia et al., 1997

Attributable risk for breast cancer, Italy

	Attributable risk percent for Italian women (95% CI)
Alcohol	10.7 (4.4-17.0)
Physical inactivity	11.6(-0.1-23.3)
Body mass index (postmenopausal)	10.2 (0.2-20.2)

Mezzetti et al., 1998

Attributable Fraction of Breast Cancer in France, 2000

Risk Factor	Attributable Fraction
Use of HRT/OCs	10.7%
Physical inactivity	10.1%
Alcohol consumption	9.4%
Reproductive factors*	5.4%
Obesity and overweight	4.8%

* Changes in reproductive factors since 1930

Boffetta et al, 2008

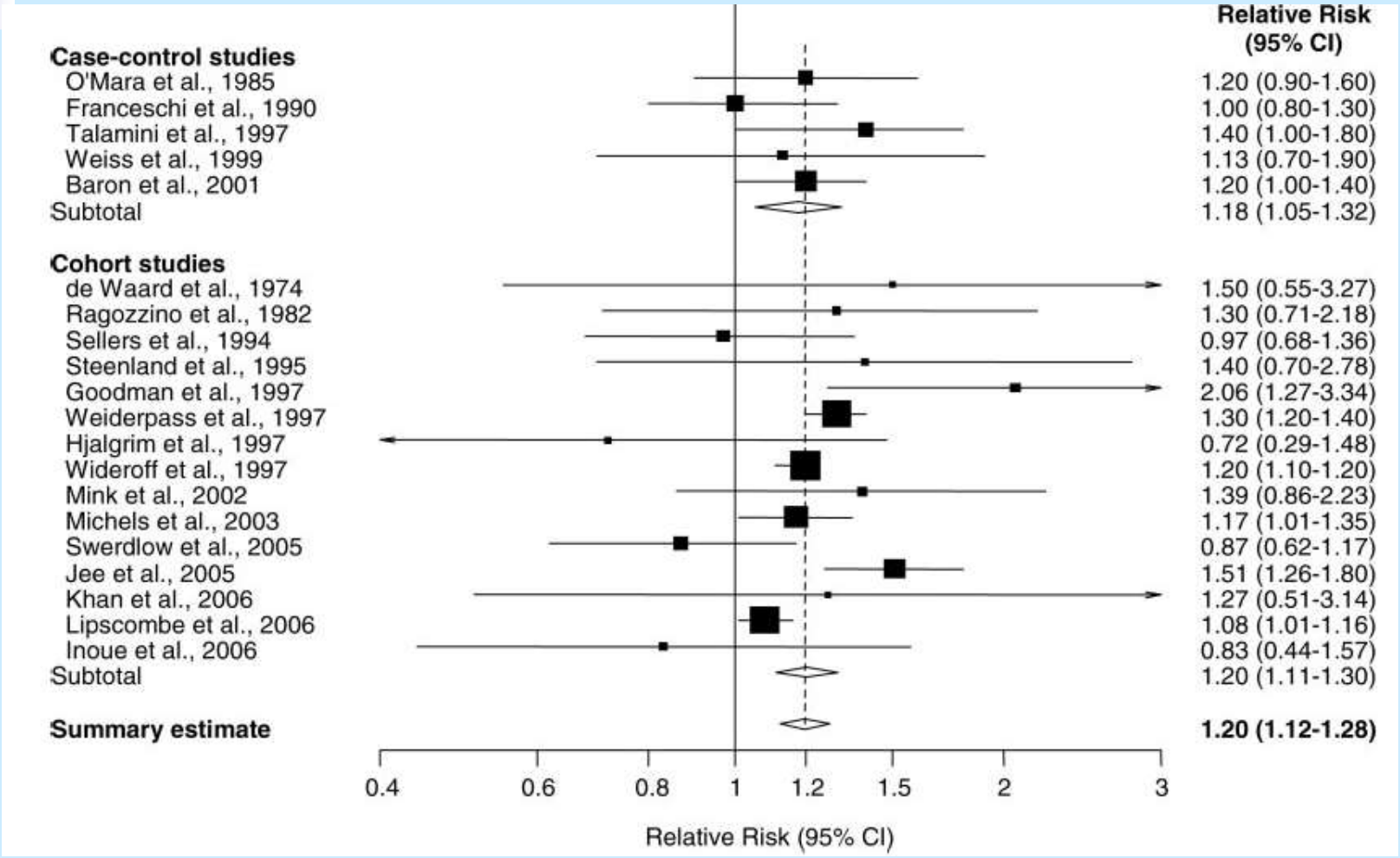
Overweight and breast cancer

Overweight and obesity are strongly related to diabetes, but also to post-menopausal breast cancer

Thus, disentangling their effect is difficult.

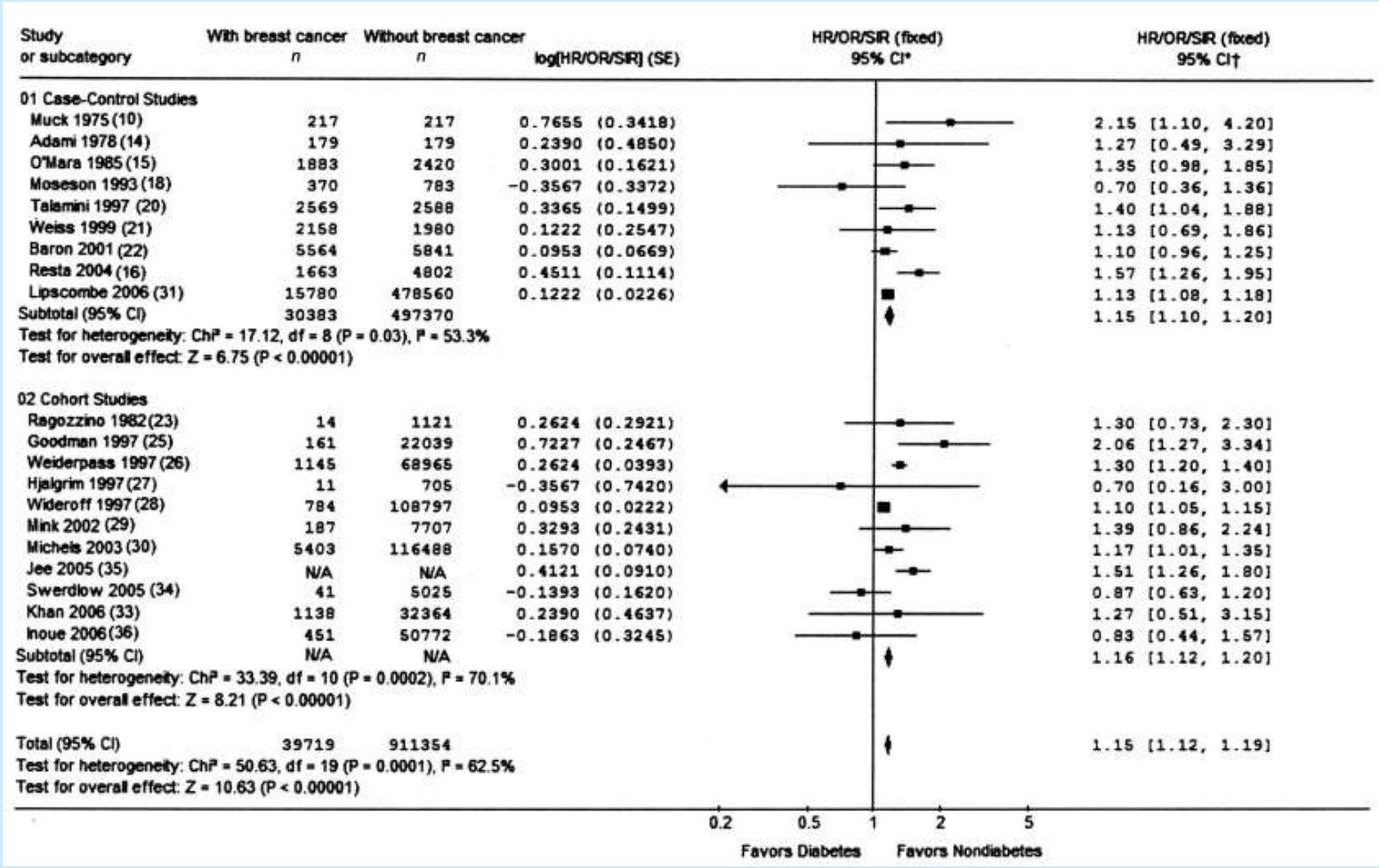
There is a residual confounding by overweight in the diabetes-breast cancer relation.

Diabetes and breast cancer: meta-analysis



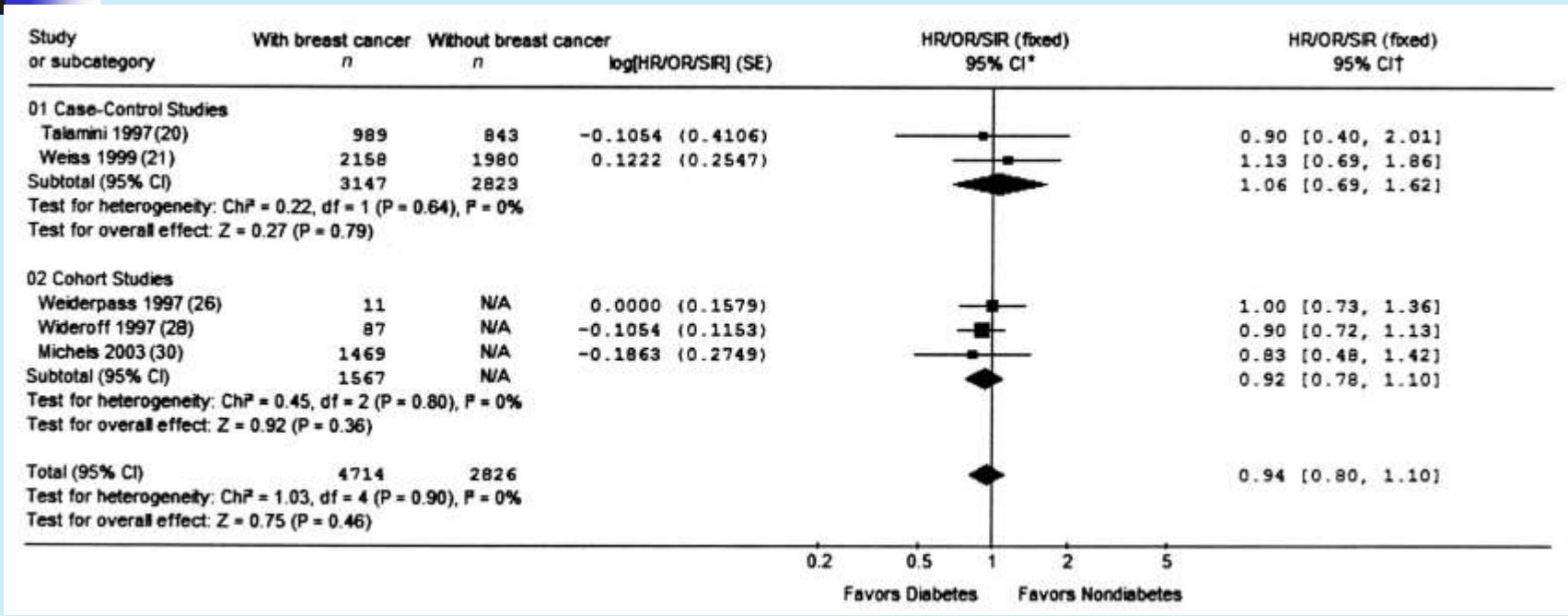
(Larsson et al., 2007)

Diabetes and breast cancer: meta-analysis



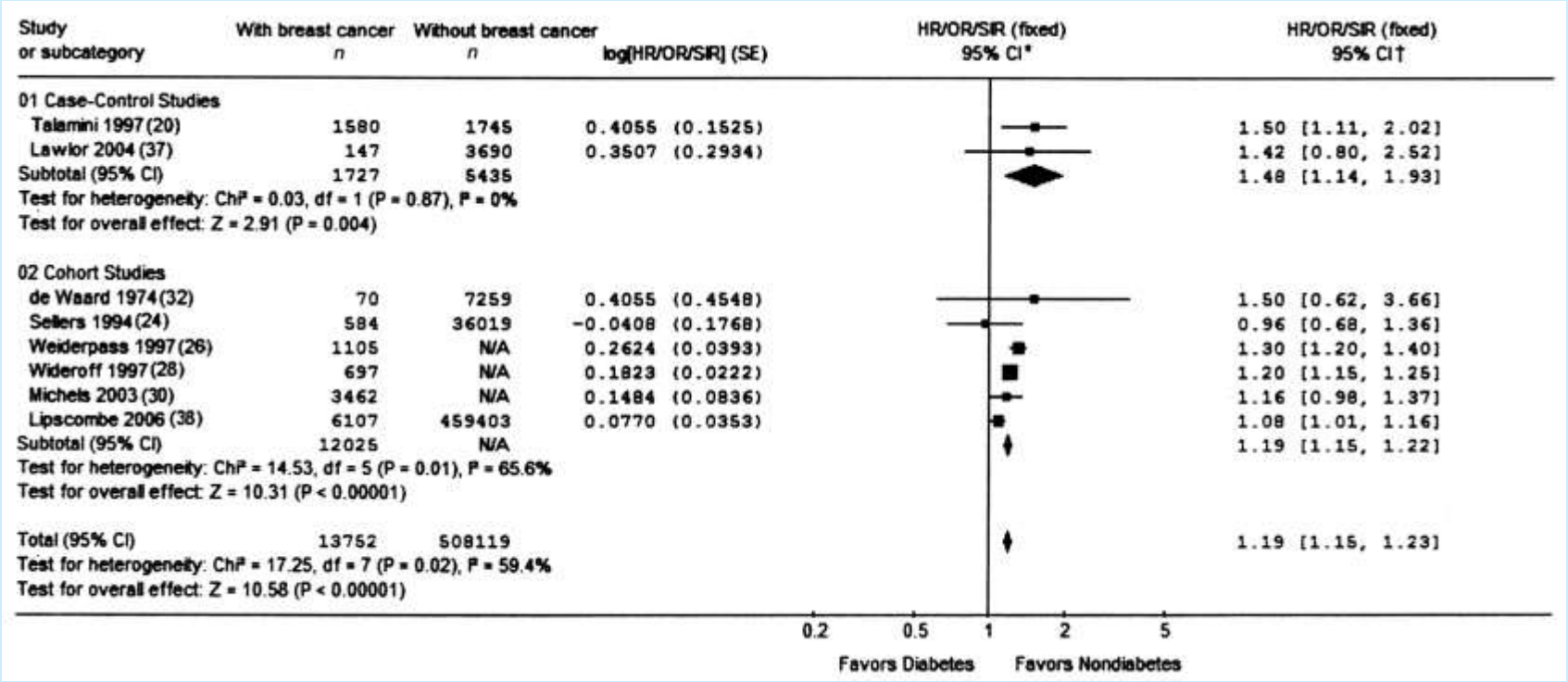
(Xue and Michels, 2007)

Diabetes and breast cancer. Pre-menopause



(Xue and Michels, 2007)

Diabetes and breast cancer. Post-menopause



(Xue and Michels, 2007)

Diabetes and breast cancer - additional data - Sweden

In a record linkage cohort study from Sweden, the RR of breast cancer in diabetic women was 1.34 (95% CI 1.28-1.46), and the RR were above unity over age 50 only (Hemminki et al., 2010).

Diabetes and breast cancer – additional data – Hispanic women

Characteristic	Cases (n = 190)		High-risk controls (n = 511)		OR[a]	(95% CI)
	N	%	*N*	%		
History of diabetes						
No	125	65.8	354	69.3	1.00	(Referent)
Yes	65	34.2	157	30.7	1.02	(0.71–1.48)
Missing	0					

(Sanderson et al., 2010)

Metabolic syndrome and breast cancer

Various aspects of the metabolic syndrome (abdominal overweight, diabetes, hypertension, hypercholesterolemia) have been related to breast cancer risk.

Diabetes and overweight show consistent association for (postmenopausal) cancer (Rosato et al, 2010).

Metabolic syndrome and breast cancer – Italian data

Component	First study (1983-1994)		Second study (1991-2007)		All
	Cases:Controls	OR (95% CI)[a]	Cases:Controls	OR (95% CI)[a]	OR (95% CI)[a]
Diabetes					
No	1878:1762	1[b]	1753:2105	1[b]	1[b]
Yes	110:108	1.00 (0.75-1.33)	128:107	1.72 (1.30-2.27)	1.33 (1.09-1.62)
Hypertension					
No	1464:1457	1[b]	1342:1617	1[b]	1[b]
Yes	524:413	1.27 (1.09-1.48)	539:595	1.14 (0.99-1.32)	1.19 (1.07-1.33)
Hyperlipidemia					
No	1763:1687	1[b]	1485:1793	1[b]	1[b]
Yes	225:183	1.10 (0.89-1.36)	396:419	1.11 (0.95-1.31)	1.08 (0.95-1.22)
Body mass index (BMI)					
<30 kg/m^2	1741:1670	1[b]	1550:1865	1[b]	1[b]
≥30 kg/m^2	247:200	1.26 (1.02-1.54)	331:347	1.28 (1.07-1.52)	1.26 (1.11-1.44)
Waist circumference[c,d]					
<88 cm			869:991	1[b]	1[b]
≥88 cm			878:944	1.17 (1.02-1.35)	1.17 (1.02-1.35)
Waist circumference[d,e]					
<88 cm or BMI < 30 kg/m^2			968:1215	1[b]	1[b]
≥88 cm or BMI ≥ 30 kg/m^2			913:997	1.28 (1.12-1.47)	1.22 (1.09-1.36)

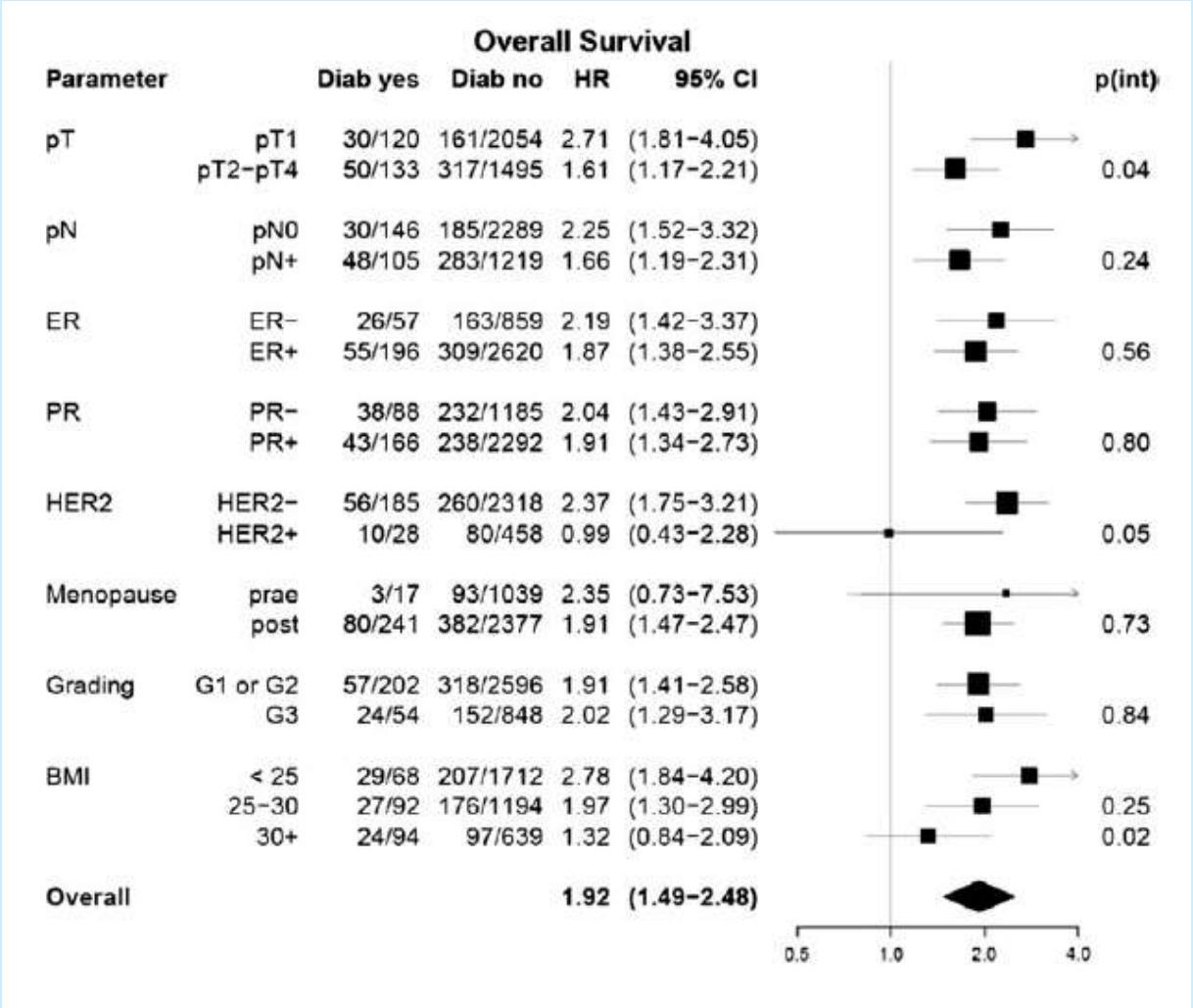
For Peer Review

(Rosato et al., 2010)

Diabetes and breast cancer

Given the moderate association (RR ÷ 1.2) any inference on causality versus residual confounding by overweight is difficult, if possible of all.

Diabetes and breast cancer survival: overall mortality



(Schrauder et al., 2010)

Diabetes and all cause mortality in women with breast cancer

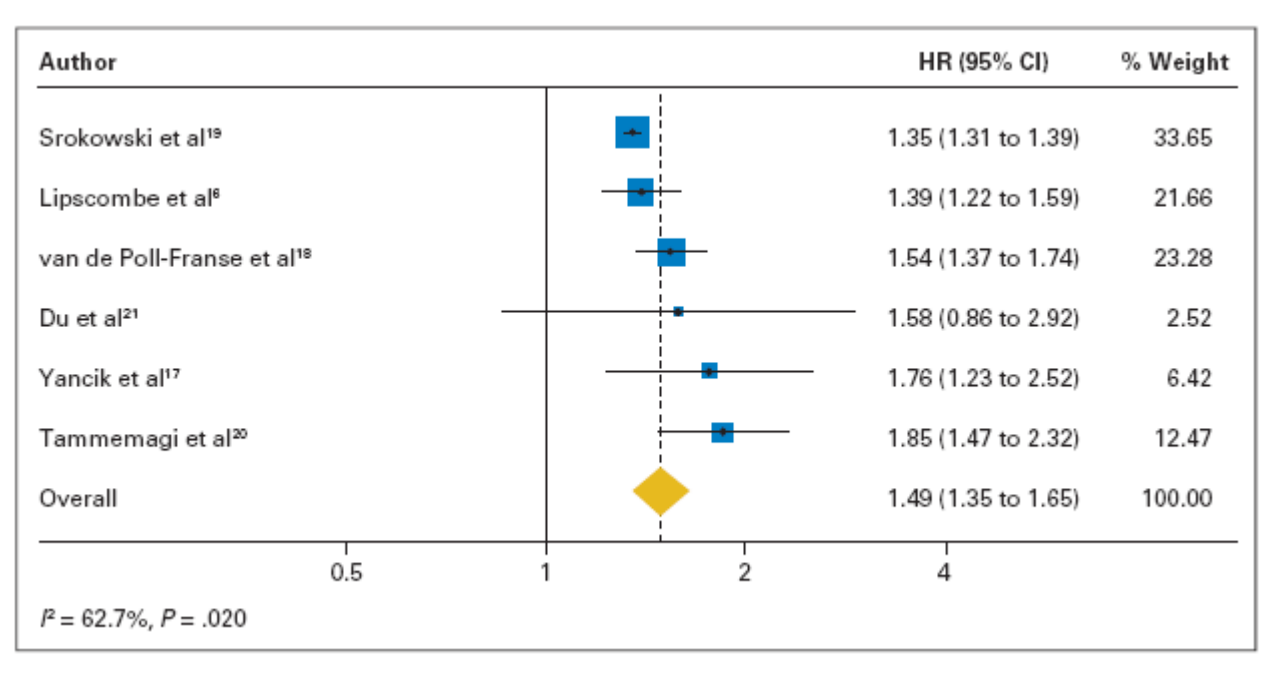


Fig 2. Meta-analysis of the effect of pre-existing diabetes on all-cause mortality in patients with breast cancer. HR, hazard ratio.

(Peairs et al., 2010)

Diabetes and cancer risk in Italy - cancers consistently associated

	Time since diagnosis of diabetes								
	<5 years			5–9 years			≥ 10 years		
Sites of cancer	*No.*[b]	*RR*	*95% CI*	*No.*[b]	*RR*	*95% CI*	*No.*[b]	*RR*	*95% CI*
Liver	13	3.9	(2.3–6.5)	9	2.9	(1.4–6.0)	21	2.6	(1.6–4.2)
Pancreas	22	3.2	(2.0–5.2)	10	2.3	(1.1–4.5)	14	1.3	(0.7–2.3)
Endometrium	67	3.7	(2.6–5.3)	32	3.1	(1.9–5.0)	50	2.0	(1.4–2.9)

Diabetes and colorectal cancer risk in Italy

Table 2 Distribution of 1225[a] cases of colon cancer, 728 cases of rectal cancer, and 4154 controls according to history of diabetes mellitus in Italy, 1992–1996

Diabetes history	Colon cancer	Rectal cancer	Controls	OR (95% CI)		
				Colon cancer	Rectal cancer	Total
Never	1159	678	3969	1[b]	1[b]	1[b]
Ever	66	50	185	1.2 (0.8–1.6)	1.5 (1.1–2.2)	1.3 (1.0–1.6)
At age ≥40 yr[c]	63	46	158	1.2 (0.9–1.7)	1.6 (1.1–2.3)	1.4 (1.1–1.7)

(La Vecchia et al., 1997)

Blood glucose concentrations and breast cancer risk in women without diabetes: a meta-analysis (Boyle et al, 2013)

In nondiabetic subjects, the risk of breast cancer associated with fasting serum glucose levels is small. Potential limitations include the fact that not all studies reported risks adjusted for adiposity and that serum glucose levels of comparison groups were variable across studies

Diabetes and cancer - summary results

Cancer type	Meta-analysis	Number of cohorts/ number of case-control studies*	Number of cancers	Risk ratio (95% CI)
Breast (all)	Larsson et al, 2007[6]	15/5	30 407	1·20 (1·12–1·28)
Premenopausal	Larsson et al, 2007[6]	Not stated	Not stated	0·91 (0·62–1·34)
Postmenopausal	Larsson et al, 2007[6]	Not stated	Not stated	1·16 (1·09–1·24)
Colorectal	Larsson et al, 2005[7]	9/6	26 306	1·30 (1·20–1·40
Endometrial	Friberg et al, 2007[8]	3/13	7596	2·10 (1·93–3·24)
Liver	El-Serag et al, 2006[9]	13/13	Not stated	2·50 (1·93–3·24)
Pancreas	Huxley et al, 2005[10]	19/17	9220	1·82 (1·71–1·94)
Non-Hodgkin lymphoma	Mitri et al, 2008[11]	5/11	Not stated	1·19 (1·07–1·32)
Bladder	Larsson et al, 2006[12]	3/7	Not stated	1·24 (1·08–1·42)
Prostate	Kasper et al, 2006[13]	12/7	20373	0·84 (0·76–0·93)

(Renehan et al., 2010)

Diabetes and cancer risk

The association between diabetes and cancer risk can be related to residual effect of overweight, but also to the IGF system, since several IGFs have been related to the risk of various human cancers, although the issue remains unsettled.

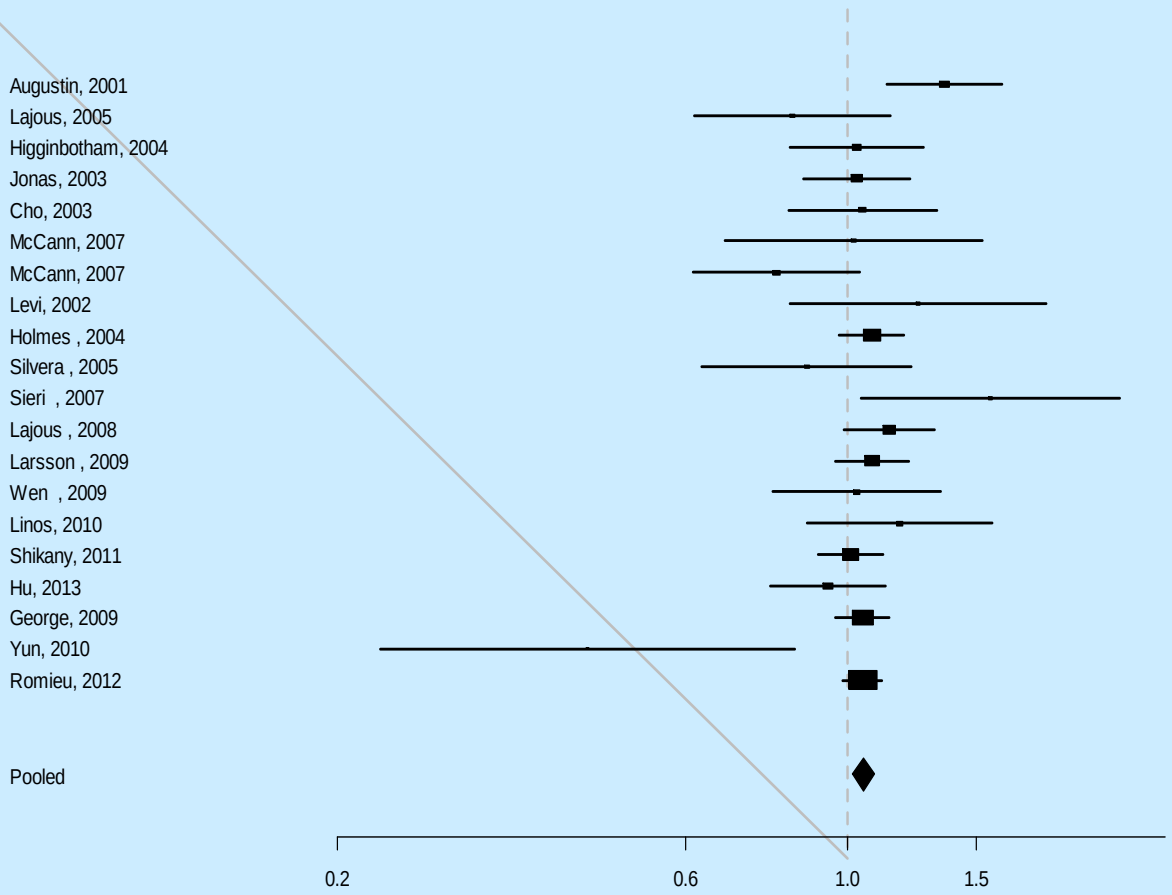
Insulin hypothesis

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

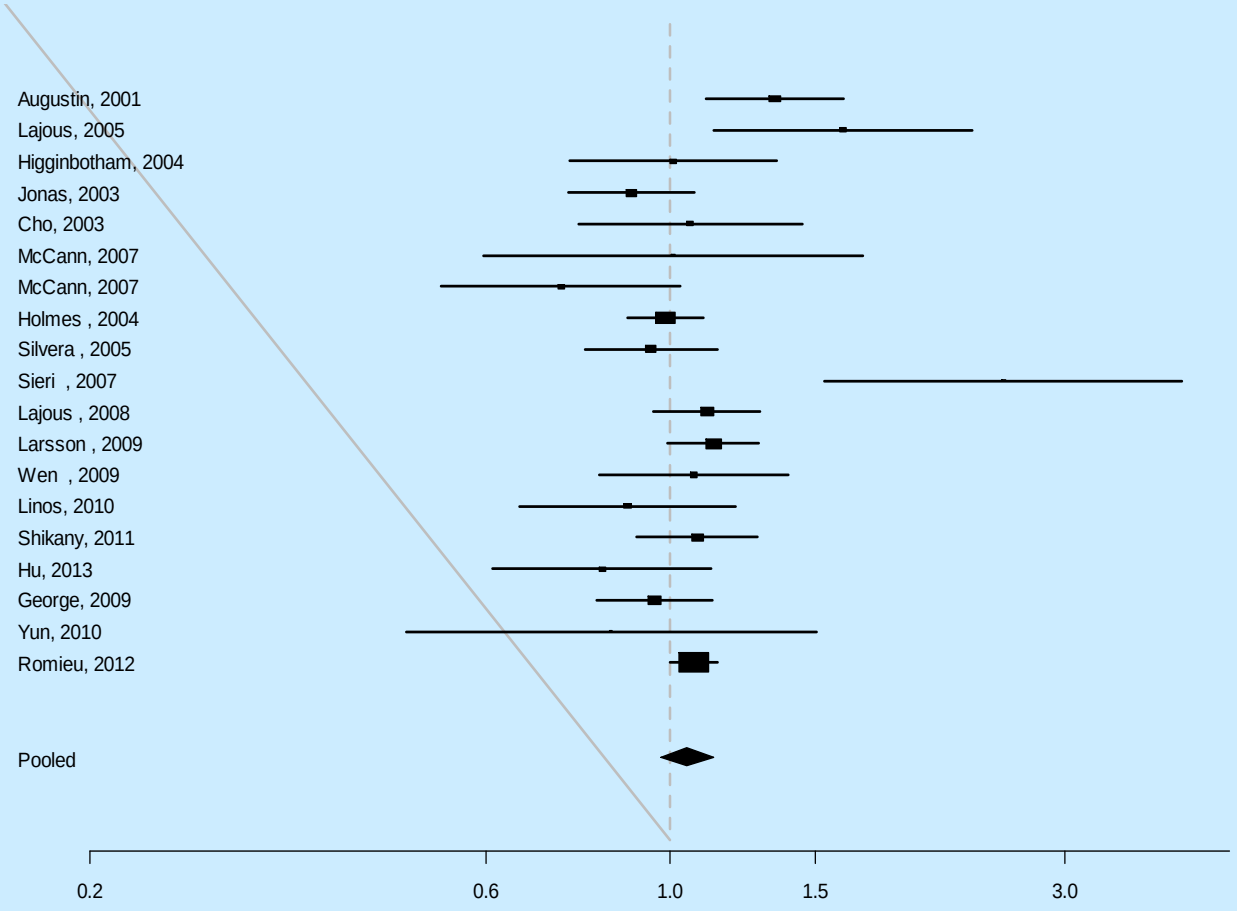
Glycemic index (GI), glycemic load (GL) and breast cancer

Glycemic load (GL), i.e. glycemic index (GI), a characteristic of carbohydrates, multiplied by the quantity of carbohydrates, has been related to the risk of a number of cancer sites, mainly of the digestive tract, but also of the breast.

Breast cancer - GI



Breast cancer - GL



Diabetes and cancer: conclusions

Diabetes and hyperglycemia are major risk factors not only for cardiovascular and metabolic diseases, but also for colorectal, liver, pancreas and endometrial cancer.

A reduced risk and prostate cancer is possible in the long term.

The association with breast cancer is moderate, and causal inference open to discussion.

Diabetes and breast cancer

Key points:

- Post menopausal breast cancer is consistentlyrelated to overweight and obesity
- Post-menopausal breast cancer is moderately related to (type 2) diabetes (RR ÷ 1.2)
- Residual confounding is possible and remain open to discussion and quantification

Diabetes and breast cancer: conclusions

The breast is not one of the cancer sites strongly related to diabetes, though an association is possible.

A modest association for post-menopausal breast cancer is possible, but residual confounding cannot be quantified and excluded.

Overweight in Italy

In Italy overweight increased from 1983 to the early 1990', and levelled off thereafter around 30% (24% in women). Prevalence of obesity remained around 7-8% during the last 20 years.

Trends in Italy are more favourable than in several other (developed) countries. Still approximately 15 million of Italian adults are overweight and 4 million obese (Gallus et al., 2006, 2013).

Recent trends in overweight ± obesity in Italy