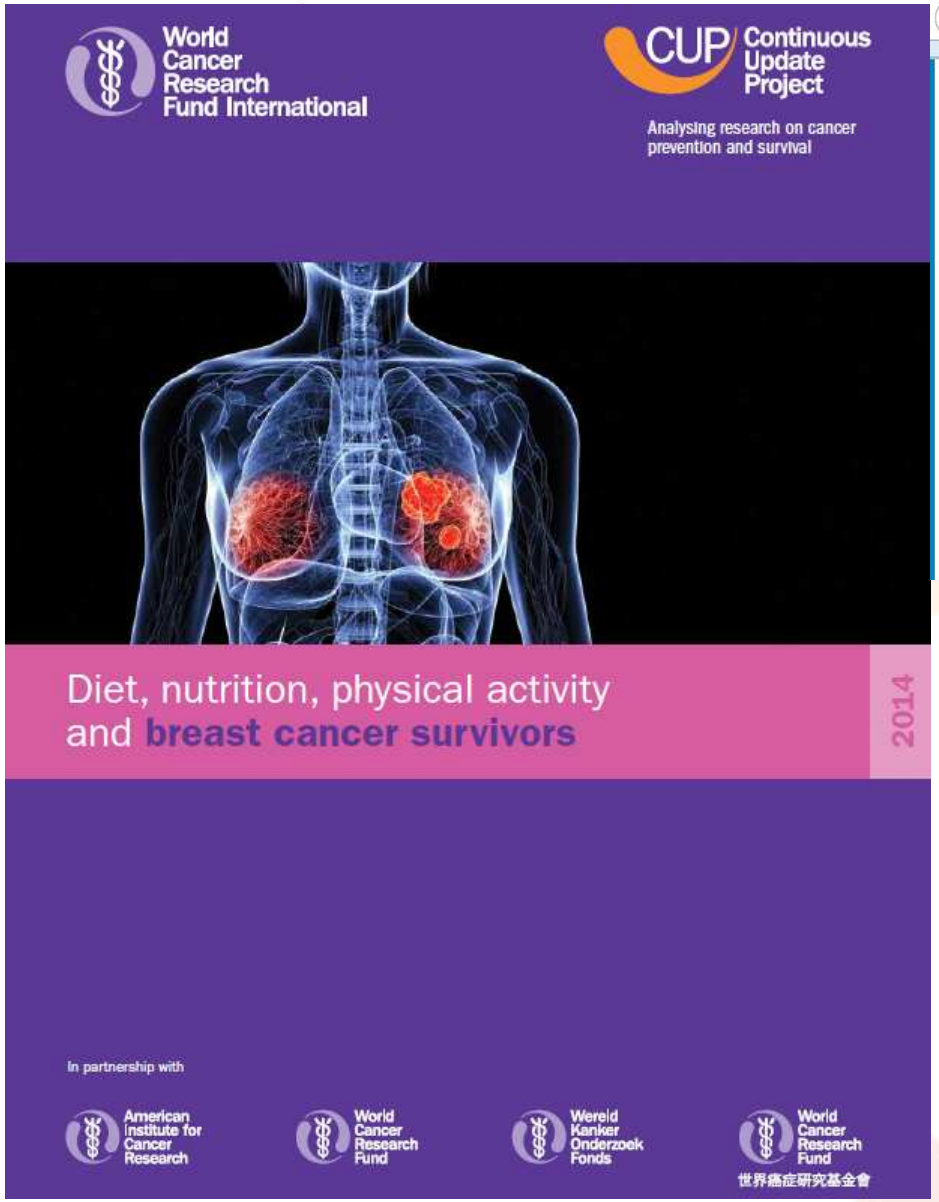
# Il ruolo del peso, dell'esercizio fisico e della dieta

Dott.ssa Paola Armaroli
AOU Città della Salute e della Scienza di Torino
S.C.Epidemiologia, Screening e Registro Tumori- CPO
Via Cavour, 31,10123 Torino, Italy

"PROGRAMMA REGIONALE DI SCREENING PER IL TUMORE DELLA MAMMELLA
PREVENZIONE SERENA - WORKSHOP 2016" Torino 1 dicembre 2016





Cancer Epidemiology 39S (2015) S1–S10

Contents lists available at ScienceDirect

Cancer Epidemiology

The International Journal of Cancer Epidemiology, Detection, and Prevention

journal homepage: www.canceepidemiology.net

# European Code against Cancer 4th Edition: 12 ways to reduce your cancer risk☆

Joachim Schüz[a,1,*], Carolina Espina[a,1], Patricia Villain[a,1], Rolando Herrero[a,1], Maria E. Leon[a,1], Silvia Minozzi[b,1], Isabelle Romieu[a,1], Nereo Segnan[b,1], Jane Wardle[c,1], Martin Wiseman[d,1], Filippo Belardelli[e,2], Douglas Bettcher[f,2], Franco Cavalli[g,2], Gauden Galea[h,2], Gilbert Lenoir[i,2], Jose M. Martin-Moreno[j,2], Florian Alexandru Nicula[k,2], Jørgen H. Olsen[l,2], Julietta Patnick[m,2], Maja Primic-Zakelj[n,2], Pekka Puska[o,2], Flora E. van Leeuwen[p,2], Otmar Wiestler[q,2], Witold Zatonski[r,2] ; Working Groups of Scientific Experts[3]

- Rigorous procedures in retrieving, assessing, interpreting the scientific evidence

to formulate recommendations based on a comprehensive, systematic and updated scientific evidence;

- criteria for Grading the evidence

- recommendations based on a consensus within a multidisciplinary panel of experts on the interpretation of the evidence

**Table 1**
Correspondence between IARC Monographs and WCRF/AICR reports in overall levels of evidence and whether the evidence was sufficient to consider a recommendation for the European Code against Cancer

| IARC monographs | WCRF/AICR reports |
|---|---|
| | Sufficient evidence for Code recommendations |
| **Group 1—carcinogenic to humans**<br>Sufficient evidence of carcinogenicity in humans.<br><br>Generally required:<br>• Several criteria of causality fulfilled [52]<br>• Strong association (large relative risk)<br>• Replication of results in several studies of same design or with different epidemiological approaches or different exposure conditions<br>• Explanation for inconsistent results, if present<br>• Graded response to exposure (not mandatory)<br>• Decline in risk after stopping exposure<br><br>Additional factors may increase confidence in causal relationship:<br>• Induction of multiple tumour types, temporality<br>• Precision of effect estimates<br>• Plausibility, coherence of overall database<br>• Biomarker data<br><br>Exceptionally with less than sufficient evidence of carcinogenicity in humans but with sufficient evidence of carcinogenicity in experimental animals and strong evidence in exposed humans of a relevant mechanism of carcinogenicity | **Convincing evidence for causal relationship**<br>Overall evidence strong enough to justify goals and recommendations to reduce cancer incidence.<br>Causal relationship highly unlikely to be modified by new evidence in foreseeable future. Generally required:<br>• Evidence from more than one study type and at least two independent cohort studies<br>• No substantial unexplained heterogeneity within or between study types or in different populations regarding presence or absence of association, or direction of effect<br>• Good quality studies to confidently exclude the possibility that the observed association results from random or systematic error, including confounding, measurement error, and selection bias<br>• Presence of a plausible biological gradient ("dose–response") in the association (gradient need not be linear or in same direction across different levels of exposure, so long as this can be explained plausibly)<br>• Strong and plausible experimental evidence, either from human studies or relevant animal models, that typical human exposures can lead to relevant cancer outcomes<br><br>**Probable evidence for causal relationship**<br>Overall evidence strong enough to justify goals and recommendations to reduce cancer incidence, but not as strong as convincing category. Generally required:<br>• Evidence from at least two independent cohort studies, or at least five case–control studies<br>• No substantial unexplained heterogeneity between or within study types in the presence or absence of an association, or direction of effect<br>• Good quality studies to confidently exclude the possibility that the observed association results from random or systematic error, including confounding, measurement error, and selection bias<br>• Evidence for biological plausibility |

a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence

## LIMITED SUGGESTIVE

***These criteria are for evidence that is too limited to permit a probable or convincing judgement, but where there is evidence suggestive of a direction of effect. The evidence may have methodological flaws, or be limited in amount, but shows a generally consistent direction of effect. This level of evidence would not be used to justify making specific recommendations.***

## LIMITED – NO CONCLUSION (any of the following)

***Evidence is so limited that no firm conclusions can be made. Evidence may be judged 'limited-no conclusion' for any of the following reasons:***

- Too few studies available
- Inconsistency of direction of effect
- Poor quality of studies

cancer-code-europe.iarc.fr/index.php/en/

International Agency for Research on Cancer

World Health Organization

English

Search...

European Code Against Cancer

HOME | 12 WAYS | ABOUT CANCER | SCIENTIFIC JUSTIFICATION | ABOUT THE CODE

# European Code Against Cancer

## 12 WAYS TO REDUCE YOUR CANCER RISK

3. Attivati per mantenere un peso sano.

4. Svolgi attività fisica ogni giorno. Limita il tempo che trascorri seduto.

5. Segui una dieta sana:
   - Consuma molti e vari cereali integrali, legumi, frutta e verdura.
   - Limita i cibi ad elevato contenuto calorico (alimenti ricchi di zuccheri o grassi) ed evita le bevande zuccherate.
   - Evita le carni conservate; limita il consumo di carni rosse e di alimenti ad elevato contenuto di sale.

6. Se bevi alcolici di qualsiasi tipo, limitane il consumo. Per prevenire il cancro è meglio evitare di bere alcolici.

10. Per le donne:
    - L'allattamento al seno riduce il rischio di cancro per la madre. Se puoi, allatta il tuo bambino.
    - La terapia ormonale sostitutiva (TOS) aumenta il rischio di alcuni tipi di cancro. Limita l'uso della TOS.

Diet, weight, physical activity have also been examined in relation to their effect on outcomes (all cause mortality, breast cancer mortality and second primary breast cancer) after breast cancer is diagnosed.

There are additional considerations that must be taken into account for observational studies of breast cancer survivors, in whom randomised controlled trials would provide the strongest evidence.

Therefore new criteria for judgement were developed for categorising the strength of evidence for causality in breast cancer survivors.

# Considerations specific to breast cancer survivors-I

## Timeframe

These timeframes take into account exposure assessment at various stages of treatment

The timeframes of exposure assessment used were:

- before primary breast cancer diagnosis: women who have not started treatment
- less than 12 months after diagnosis of primary breast cancer: women undergoing treatment
- 12 months or more after diagnosis of primary breast cancer: women who have finished treatment.

# Considerations specific to breast cancer survivors-II

## Treatment

Treatment varies by breast tumour type and spread, and patient characteristics.

The type and amount of treatment can have a greater effect on survival than most exposures related to diet, nutrition, and physical activity, and is likely a confounding factor.

# Considerations specific to breast cancer survivors-III

## Time periods and changes in treatments

Due to improved knowledge regarding tumour type, new treatment regimens have changed the expected effect of treatment and thus breast cancer mortality.
Treatment regimens vary according to time periods, country, and socio-economic status within countries.

## Reverse causation

An exposure being studied may be a result of the diagnosis (or treatment), and not the other way around.

# Considerations specific to breast cancer survivors-IV

## Mortality and breast cancer subtype

Pre-existing disease, and some specific subtypes of breast cancer are more likely to lead to early (within the first two years after diagnosis) recurrence or death. If a survivor cohort is assembled a long time after diagnosis, such women at high risk for mortality may not be included.

Advances in treatment coupled with earlier diagnosis have led to longer survival beyond five years, up to 10 years and beyond. Therefore, it is important to consider survival in terms both of the cancer subtype, as well as of the time point after diagnosis when data collection occurs and follow-up begins.

# Considerations specific to breast cancer survivors-V

## Randomised Controlled Trials (RCTs) and cohort data

Well-conducted RCTs may provide strong evidence; however patients included in RCTs may not be representative of the wider population of breast cancer survivors. Survivors who do not enter RCTs may be sicker, have different lifestyles and could have lower survival rates.

Cohort studies with large numbers of cases and a high response to follow-up may have better generalisability. However, in order to provide strong evidence cohort data must be fully adjusted for potential confounders such as tumour type, type of treatment, amount of treatment received, and the dissemination of disease, and this is not always possible

**Outcomes:** all cause mortality, cause specific breast cancer mortality, and second primary breast cancer

**Study population:** pre and postmenopausal women with a diagnosis of in situ or invasive breast cancer

The CUP-Breast Cancer Survivors SLR included studies published up to 30 June 2012 (update in progress, publications up to June 2013)
The total number of women in the 85 studies reviewed was 164,416; total number of deaths in the studies 42,572

The ECAC: systematic search up to 31/1/2013 and studies published after the deadline if proposed by the experts and if changing the body of evidence

# Body fatness

Body mass index (BMI), waist and hip circumference and waist hip ratio as measures of body fatness.

These anthropometrical measures are imperfect and cannot distinguish between lean mass and fat mass

# Body fatness

Chan et al, Annals of Oncology 25: 1901–1914, 2014

82 studies, including 213 075 breast cancer survivors with 41 477 deaths (23 182 from breast cancer) were identified.

For before, <12 months after, and 12 months or more after breast cancer diagnosis, compared with normal weight (BMI 18.5-25.0kg/m$^2$ women), obese (BMI>30) women

had 41%, 23%, and 21% higher risk for total mortality,

and 35%, 25%, and 68% increased risk for breast cancer mortality.

The findings were supported by the positive associations observed in the linear dose–response meta-analysis

# BMI and total mortality

deaths=6358
statistically significant
**17% increased risk** per 5 kg/m$^2$

deaths=6020
statistically significant
**11% increased risk** per 5 kg/m$^2$

deaths=1703
statistically significant
**8% increased risk** per 5 kg/m$^2$

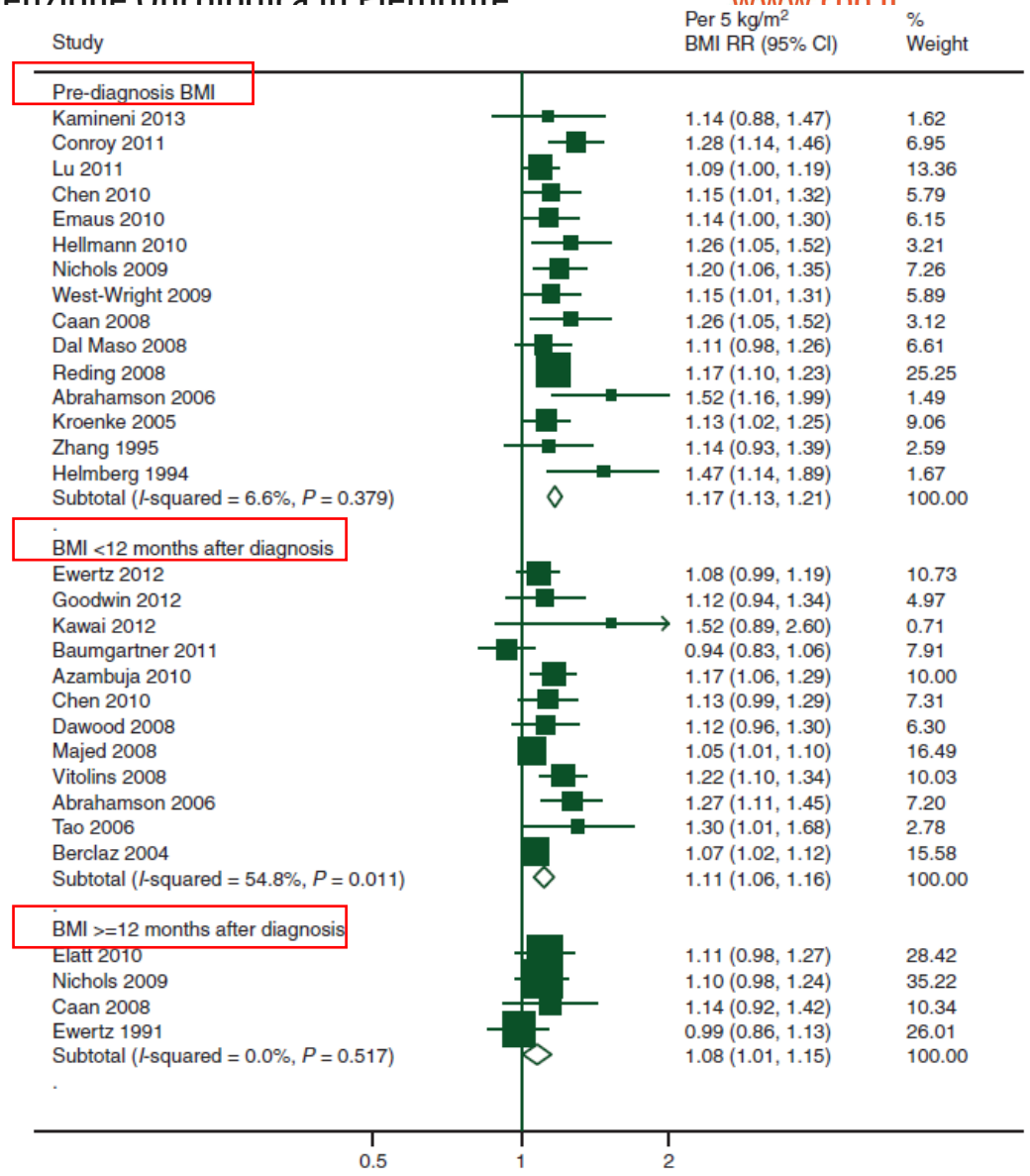


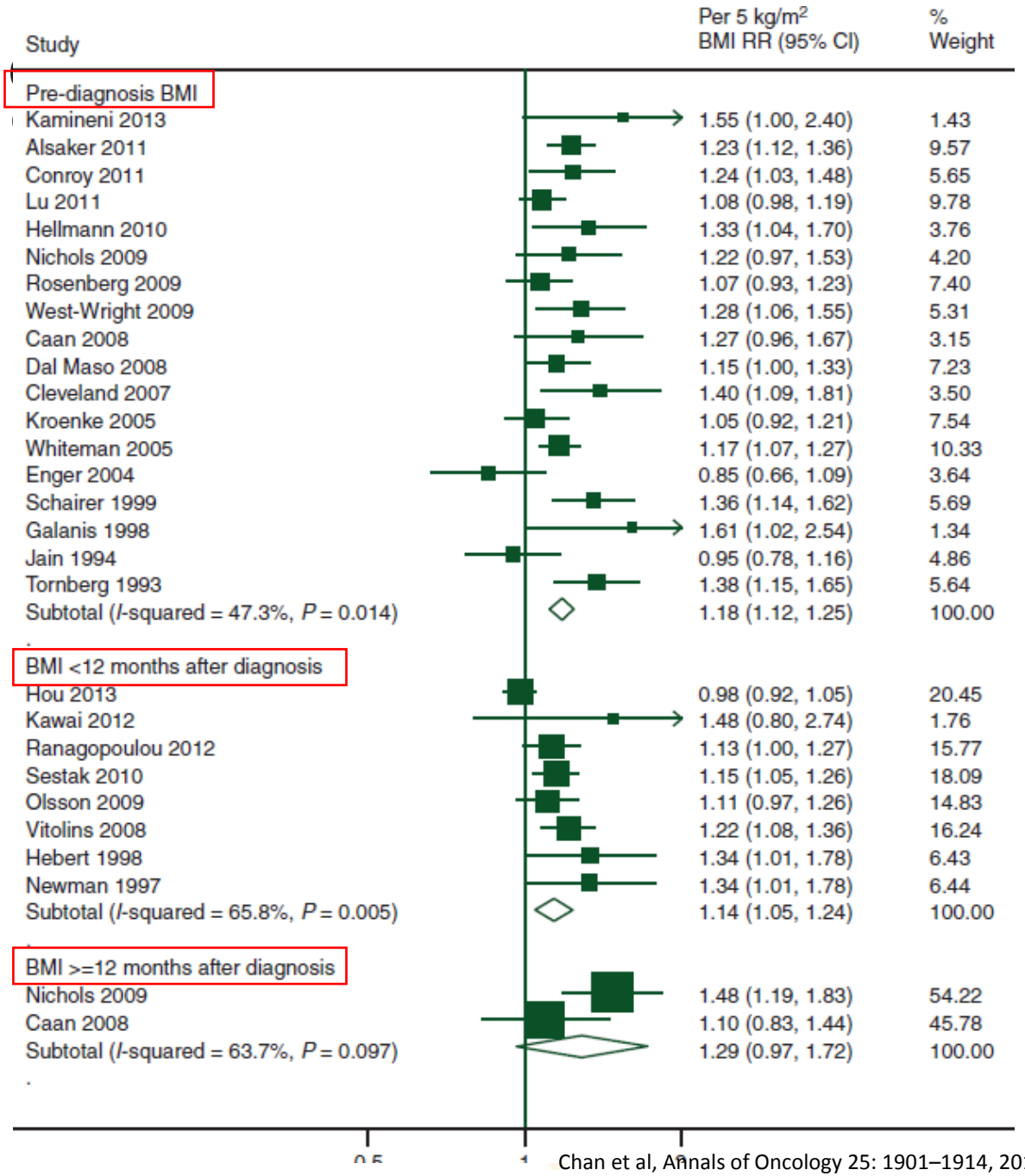

**Figure 4.** Linear dose–response meta-analysis of BMI and total mortality. Chan et al, Annals of Oncology 25: 1901–1914, 2014

# BMI and breast cancer mortality

BC deaths= 5262
statistically significant
**18% increased risk** per 5 kg/m$^2$

BC deaths=3857
statistically significant
**14% increased risk** per 5 kg/m$^2$

BC deaths=220
not statistically significant
**29% increased risk** per 5 kg/m$^2$




Chan et al, Annals of Oncology 25: 1901–1914, 2014

Increased risks of mortality were observed in the meta-analyses by menopausal status.

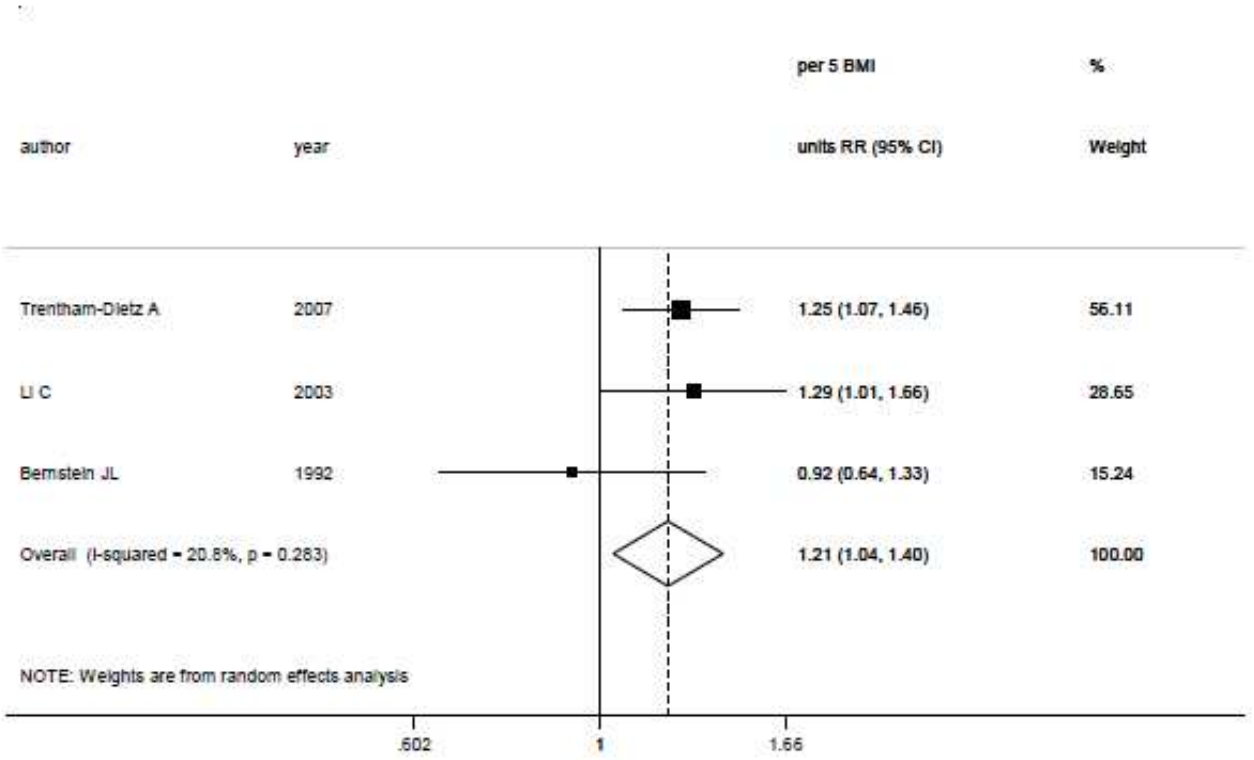
For BMI before diagnosis and total mortality, the summary RRs for obese versus normal weight were 1.75 (95% CI 1.26–2.41, I2 = 70%, P < 0.01, 7 studies) in women with pre-menopausal breast cancer and 1.34 (95% CI 1.18–1.53, I2 = 27%, P = 0.20, 9 studies) in women with postmenopausal breast cancer

Chan et al, Annals of Oncology 25: 1901–1914, 2014

# Second primary BC/contralateral BC and BMI, before diagnosis

n= 701
statistically
significant
**21% increased**
**risk** per 5 kg/m$^2$

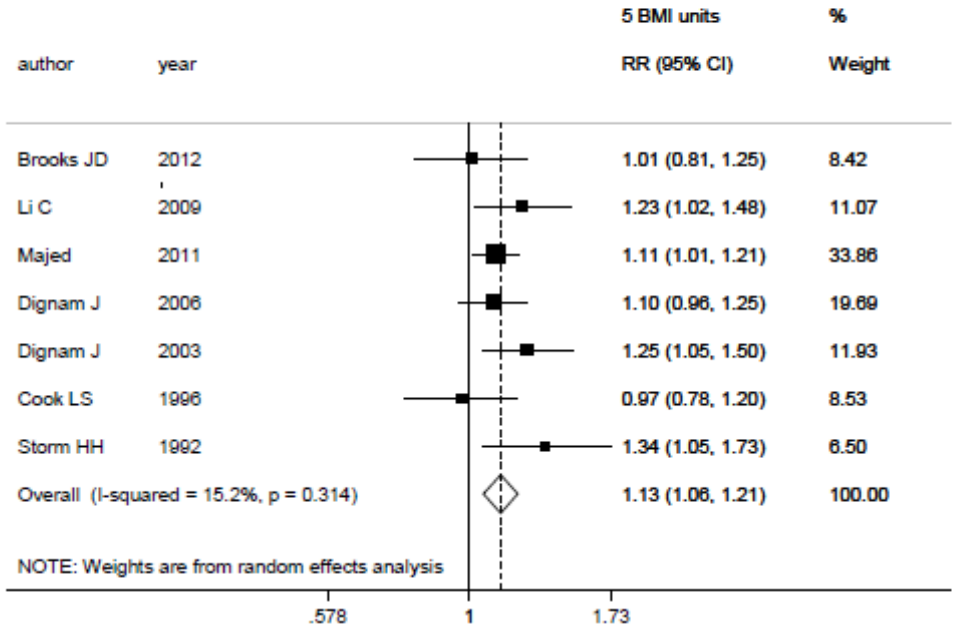
**Figure 127 Linear dose-response meta-analysis of before diagnosis BMI and second primary breast cancer/contralateral breast cancer**



# Second primary BC/contralateral BC and BMI, less than 12 months after

n=3186
statistically significant
13% increased risk per 5kg/m2

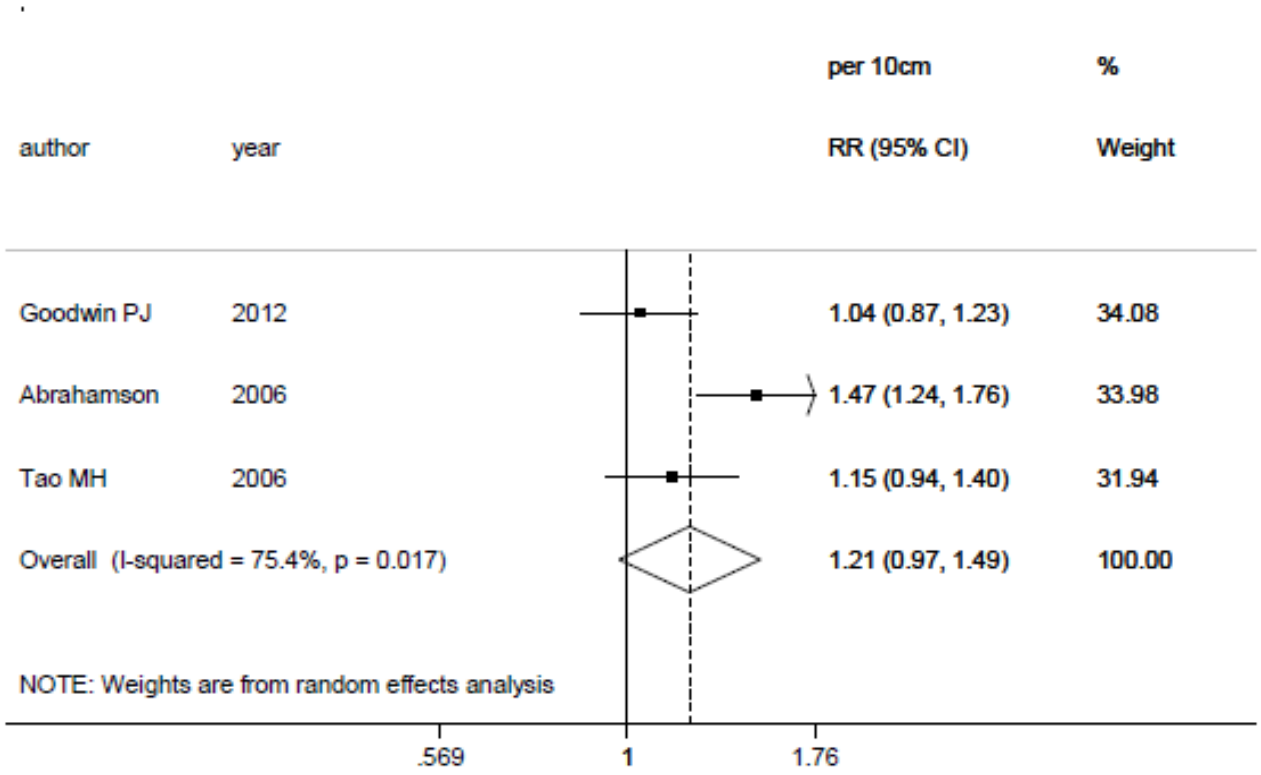
**Figure 130 Linear dose-response meta-analysis of BMI less than 12 months after diagnosis and contralateral breast cancer**



# Total mortality and Waist circumference, less than 12 months after

N=664
Not statistically significant
**21% increased risk**
per 10 cm

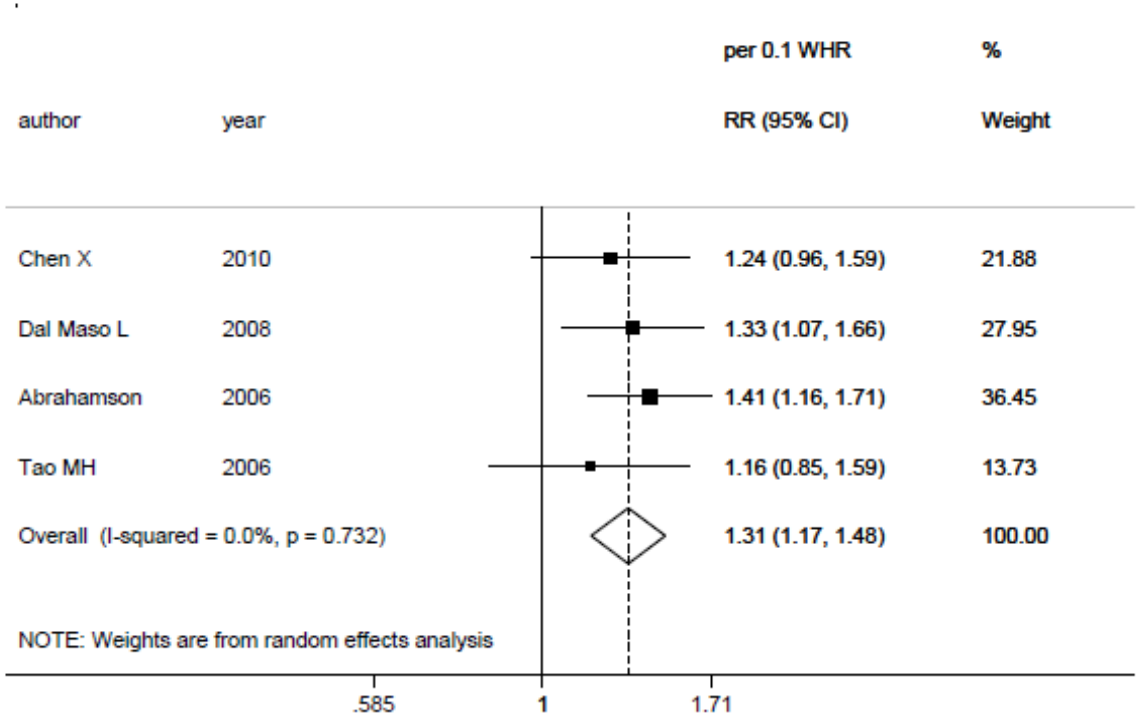
**Figure 150 Linear dose-response meta-analysis of waist circumference less than 12 months after diagnosis and total mortality**



# Total mortality and waist-hip ratio, less than 12 months after

n=1475
statistically
significant
31% increased risk
per 0.1 unit

**Figure 153 Linear dose-response meta-analysis of waist-hip ratio less than 12 months after diagnosis and total mortality**



## CUP Panel's conclusions

There is generally consistent evidence of a positive association between greater body fatness (which the CUP Panel interprets to be marked by BMI) and all cause mortality, breast cancer mortality and development of second primary breast cancer. However, it is not clear to what extent individual studies have fully adjusted for potential confounders such as the tumour type, type of treatment, amount of treatment received, and the dissemination of the disease. The evidence on waist circumference, hip circumference and waist-hip ratio was consistent with that of BMI, but was limited.

Chan et al, Annals of Oncology 25: 1901–1914, 2014

RCTs are needed to test interventions for weight loss and maintenance on survival in women with breast cancer.
The present systematic literature review and meta-analysis extends and confirms the associations of obesity with an unfavourable overall and breast cancer survival in pre and post-menopausal breast cancer, regardless of when BMI is ascertained.

Given the comparable elevated risks with obesity in the development (for postmenopausal women) and prognosis of breast cancer, and the complications with cancer treatment and other obesity-related co-morbidities,
it is prudent to maintain a healthy body weight (BMI 18.5–<25.0 kg/m2) throughout life.

# Physical activity

Total physical activity was defined as the physical activities in different types of activities, e.g. occupational, recreational and household activities; or recreational and household activities; or non occupational activity when it includes walking time, stair climbing and city block walking, since these activities are not considered as recreational activity but part of the daily routine activities.

Recreational physical activity was defined as physical activity in leisure time.

Vigorous physical activity was any type of vigorous activity in recreational and non-recreational activities.

# Total, BC mortality and physical activity (total, recreational )(highest vs lowest levels),

not statistically significant
20% risk reduction

statistically significant
25% risk reduction

statistically significant
37% risk reduction

not statistically significant
19% risk reduction

statistically significant
39% risk reduction

not statistically significant
29% risk reduction

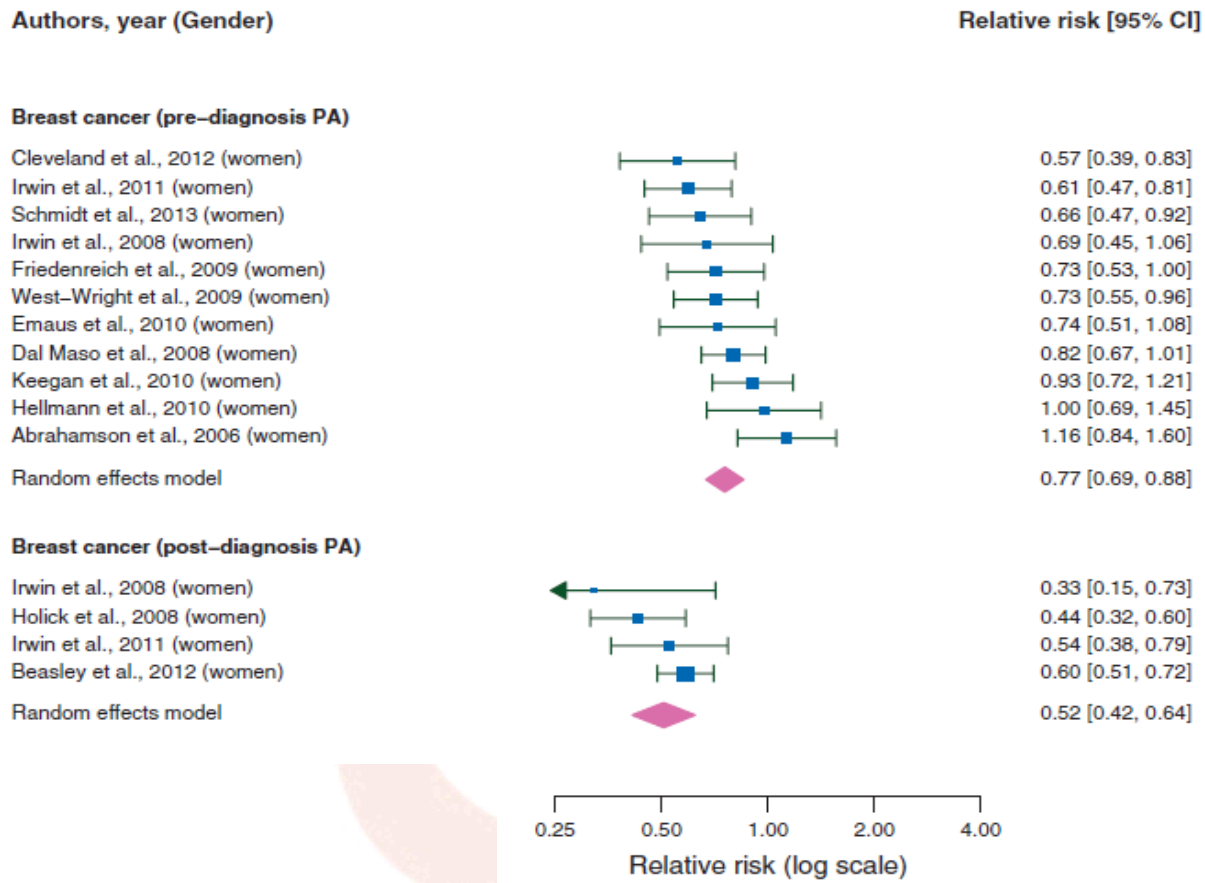
| | Total mortality | | | Breast cancer mortality | | |
|---|---|---|---|---|---|---|
| **Comparison** | **No. of studies** | **No. of events in studies** | **RR (95% CI) $I^2$, $P_{heterogeneity}$** | **No. of studies** | **No. of events in studies** | **RR (95% CI) $I^2$, $P_{heterogeneity}$** |
| **Total physical activity before breast cancer diagnosis** | | | | | | |
| Highest vs. lowest | 2 | 505 | 0.83 (0.62-1.12) 22.7%, p = 0.25 | 2 | 338 | 0.80 (0.59-1.10) 0%, p = 0.88 |
| **Recreational physical activity before breast cancer diagnosis** | | | | | | |
| Highest vs. lowest | 8 | 2892 | 0.74 (0.67-0.83) 5%, p=0.39 | 7 | 1750 | 0.76 (0.61-0.95) 48.7%, p = 0.06 |
| **Total physical activity 12 months or more after breast cancer diagnosis** | | | | | | |
| Highest vs. lowest | 3 | 514 | 0.63 (0.41-0.97) 44.1%, p = 0.16 | 2 | 217 | 0.81(0.48-1.36) 0%, p = 0.63 |
| Per 10 MET-h/week | 3 | 514 | 0.90 (0.79-1.03) 78.7%, p = 0.009 | - | - | - |
| **Recreational activity 12 months or more after breast cancer diagnosis** | | | | | | |
| Highest vs. lowest | 5 | 2337 | 0.61 (0.50-0.74) 45.8%, p = 0.12 | 2 | 392 | 0.71 (0.45-1.12) 33%, p = 0.22 |
| Per 10 MET-h/week | 5 | 2337 | 0.81 (0.73-0.90) 63.8%, p = 0.03 | - | - | - |

* No studies on second primary cancers were included in the meta-analyses.

# Total mortality and physical activity (highest vs lowest levels), pre-postdiagnosis

statistically significant
23% risk reduction

statistically significant
48% risk reduction

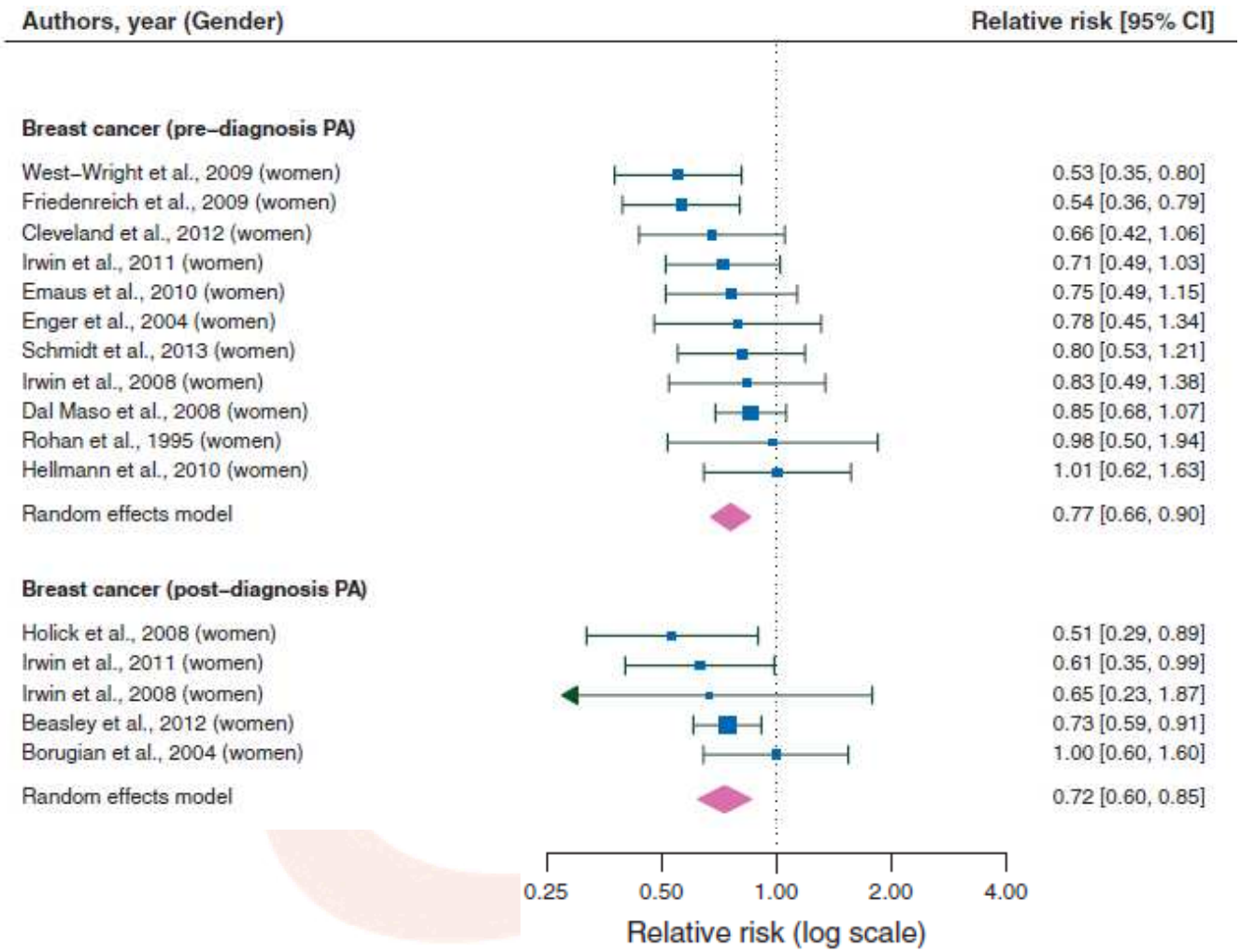



Schmid et al Association between physical activity and mortality among breast cancer and colorectal cancer survivors: a systematic review and meta-analysis Annals of Oncology 25: 1293–1311, 2014

# BC mortality and physical activity (highest vs lowest levels), pre-postdiagnosis

statistically significant
23% risk reduction

statistically significant
28% risk reduction




Schmid et al Association between physical activity and mortality among breast cancer and colorectal cancer survivors: a systematic review and meta-analysis Annals of Oncology 25: 1293–1311, 2014

## Stratification by BMI, menopausal status, and tumor ER status.

The association between pre- or post-diagnosis physical activity and total mortality among breast cancer survivors did not differ according to BMI, menopausal status, or tumor ER status.

Schmid et al Association between physical activity and mortality among breast cancer and colorectal cancer survivors: a systematic review and meta-analysis Annals of Oncology 25: 1293–1311, 2014

# Dose–response relation between physical activity and total mortality and cancer mortality.

MET: Metabolic equivalent per task, as an index of the intensity of activities

Each 5, 10, or 15 MET-h/week increase in pre-diagnosis physical activity was related to a 7% (95% CI = 2–12%), 13% (95% CI = 4–21%), and 19% (95% CI = 6–30%) reduction in risk of total mortality among breast cancer survivors, respectively. Similar estimates for cancer mortality

Each 5, 10, or 15 METh/ week increase in post-diagnosis physical activity was associated with reduction in risk of:

13% (95% CI = 6–20%), 24% (95% CI = 11– 36%), and 34% (95% CI = 16–38%) for total mortality, respectively.

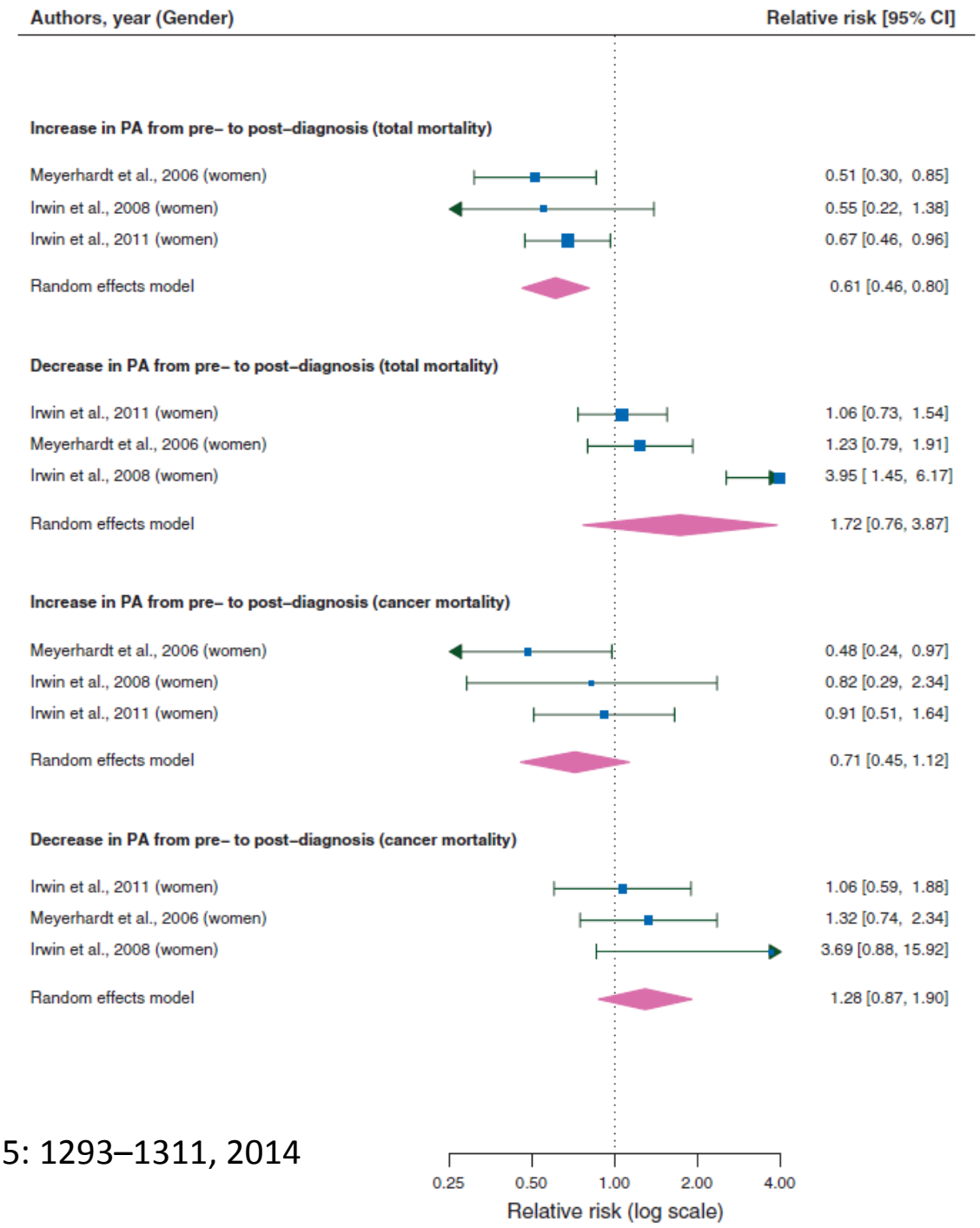
6% (95% CI = 3–8%), 11% (95% CI = 6–15%), and 16% (95% CI = 9–22%) for cancer mortality, respectively.

Schmid et al Association between physical activity and mortality among breast cancer and colorectal cancer survivors: a systematic review and meta-analysis Annals of Oncology 25: 1293–1311, 2014

# Change in physical activity from pre- to post- diagnosis

Breast or colorectal cancer survivors

(comparison: who did not change, o inactive/insuff active before diagnosis)




Schmid et al Annals of Oncology 25: 1293–1311, 2014

Randomized controlled trials show a beneficial effect of physical activity on body composition, physical fitness, quality of life, anxiety, and self-esteem in cancer survivors

## CUP Panel's conclusions

The evidence was generally consistent showing an inverse association between physical activity and all cause mortality and breast cancer mortality. It was not clear to what extent individual studies have fully adjusted for potential confounders such as the tumour type, type of treatment, amount of treatment received, and the dissemination of the disease.

Schmid et al Association between physical activity and mortality among breast cancer and colorectal cancer survivors: a systematic review and meta-analysis Annals of Oncology 25: 1293–1311, 2014

The approximate equivalent of 150 min of at least moderate physical activity per week:
- after cancer diagnosis was associated with a 24% reduced risk of total mortality;
- performed pre-diagnosis was associated with a 13% reduced of total mortality.

The apparent protection from total mortality was observed in analyses with and without adjustments for tumor stage, cancer treatment, smoking, and adiposity, and it was evident in both large and small studies, in studies using self-reported and interview-based physical activity assessments, and in studies from different countries. The benefit was evident for both lean and overweight women, for pre- and postmenopausal women, and for ER positive and negative tumors.
These findings strongly support current physical activity guidelines for cancer survivors, which endorse 150 min of moderate activity per week

## Diet

Diet may also play a role in surviving a breast cancer diagnosis, but there are relatively few studies on diet and survival after breast cancer. The studies that are available indicate:

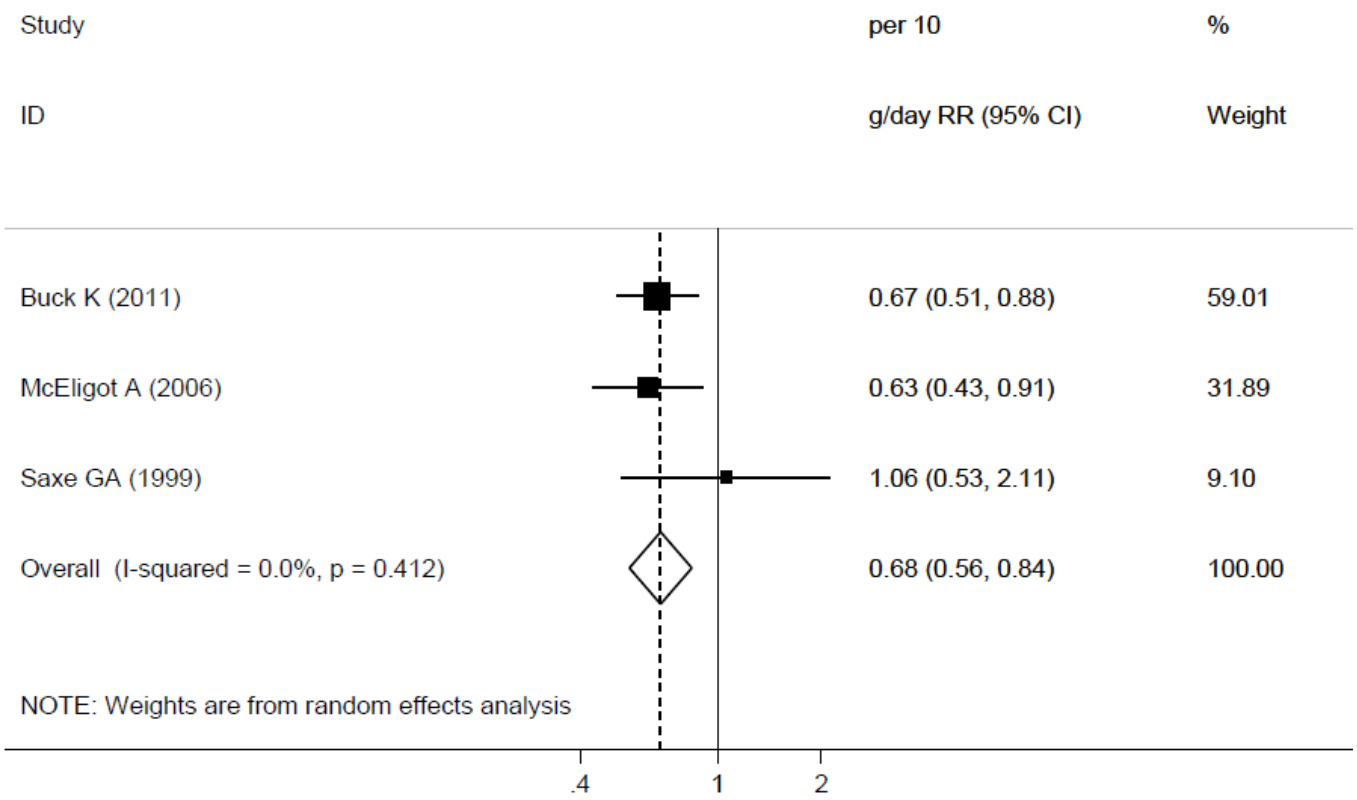
- Women who eat more foods containing fibre - both before and after diagnosis – may have a lower risk of dying from breast cancer.
- Breast cancer survivors who eat more foods containing soy *after* diagnosis may have a lower risk of dying from the disease.
- Women consuming a diet high in fat and saturated fat *before* developing the disease may have an increased risk of dying *following* a diagnosis of breast cancer.

More research is needed to investigate these links in order to confirm whether these foods affect survival after breast cancer.

CUP's conclusions: the evidence was sparse but generally consistent

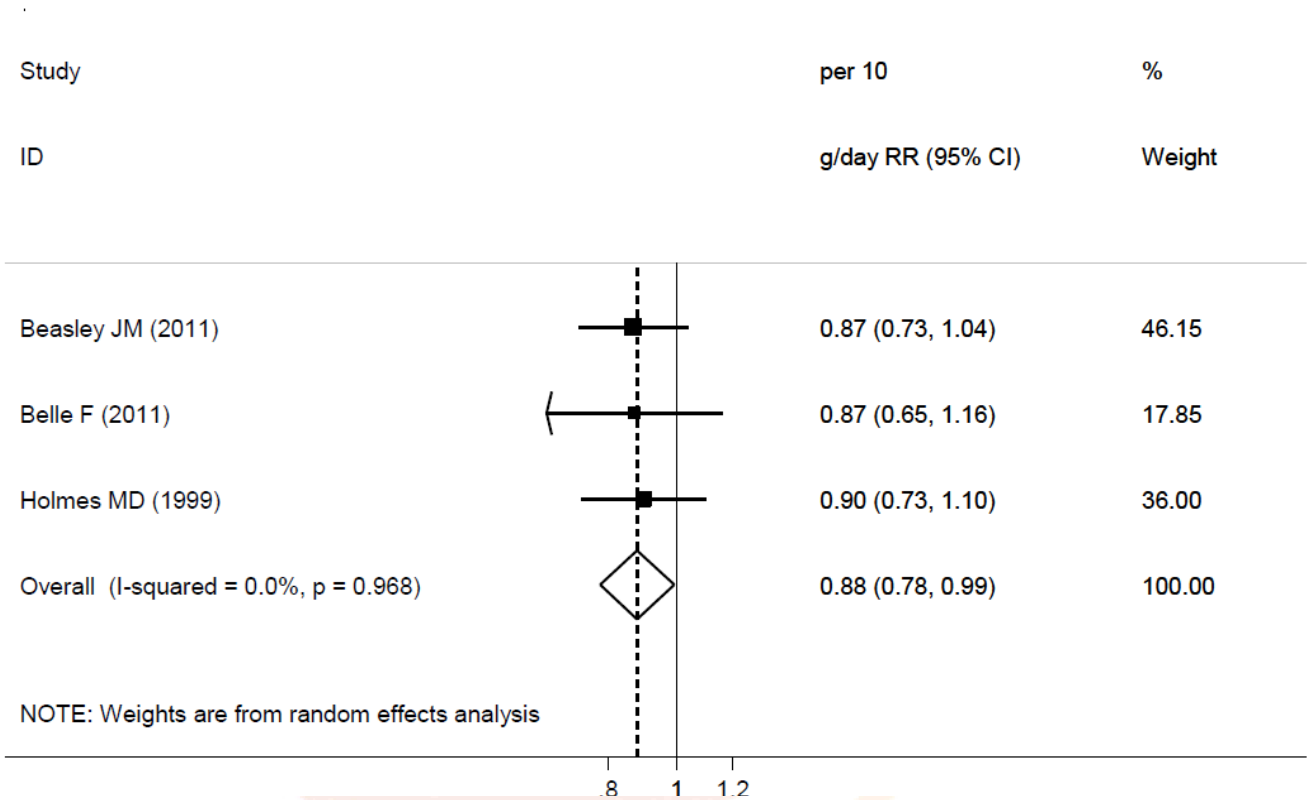
# Total mortality and foods containing fibre, before

n=443
statistically
significant
32% risk reduction
per 10 g per day



# Total mortality and foods containing fibre, 12 months or more

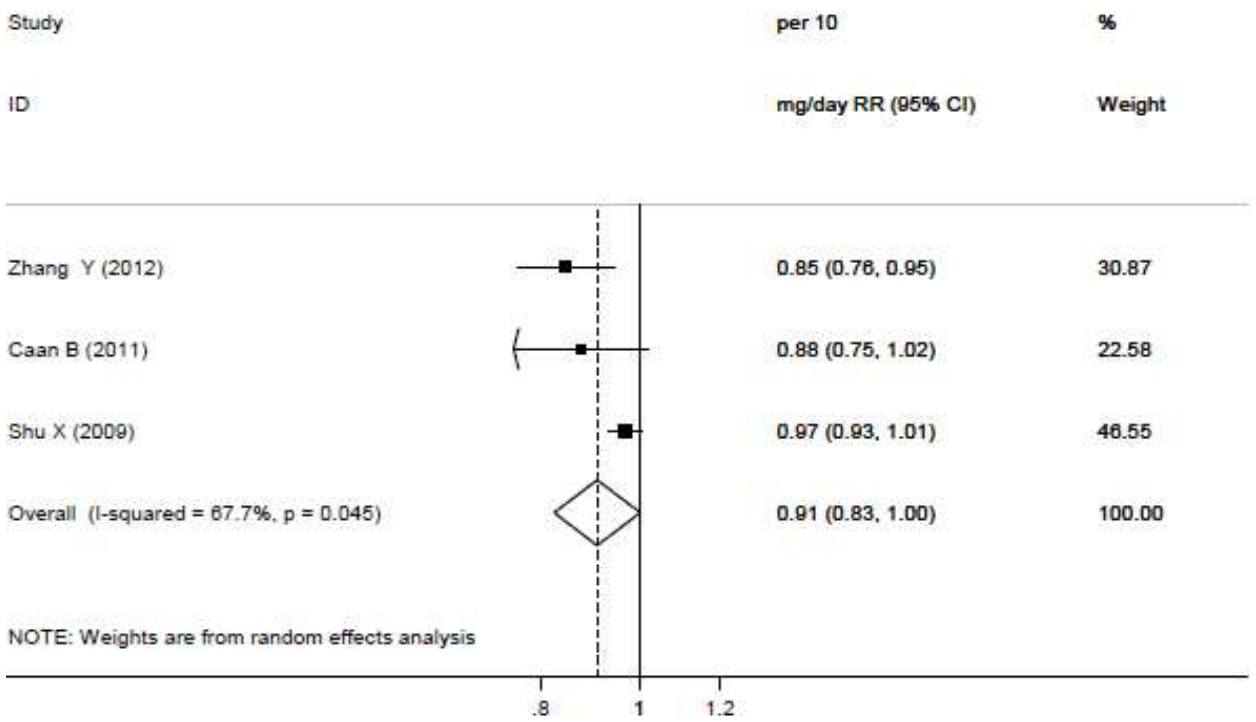
n=1092
statistically
significant
12% risk reduction
per 10 g per day




CUP's conclusions: the evidence was sparse but generally consistent

# Total mortality and foods containing soy (isoflavone intake), 12 months or more

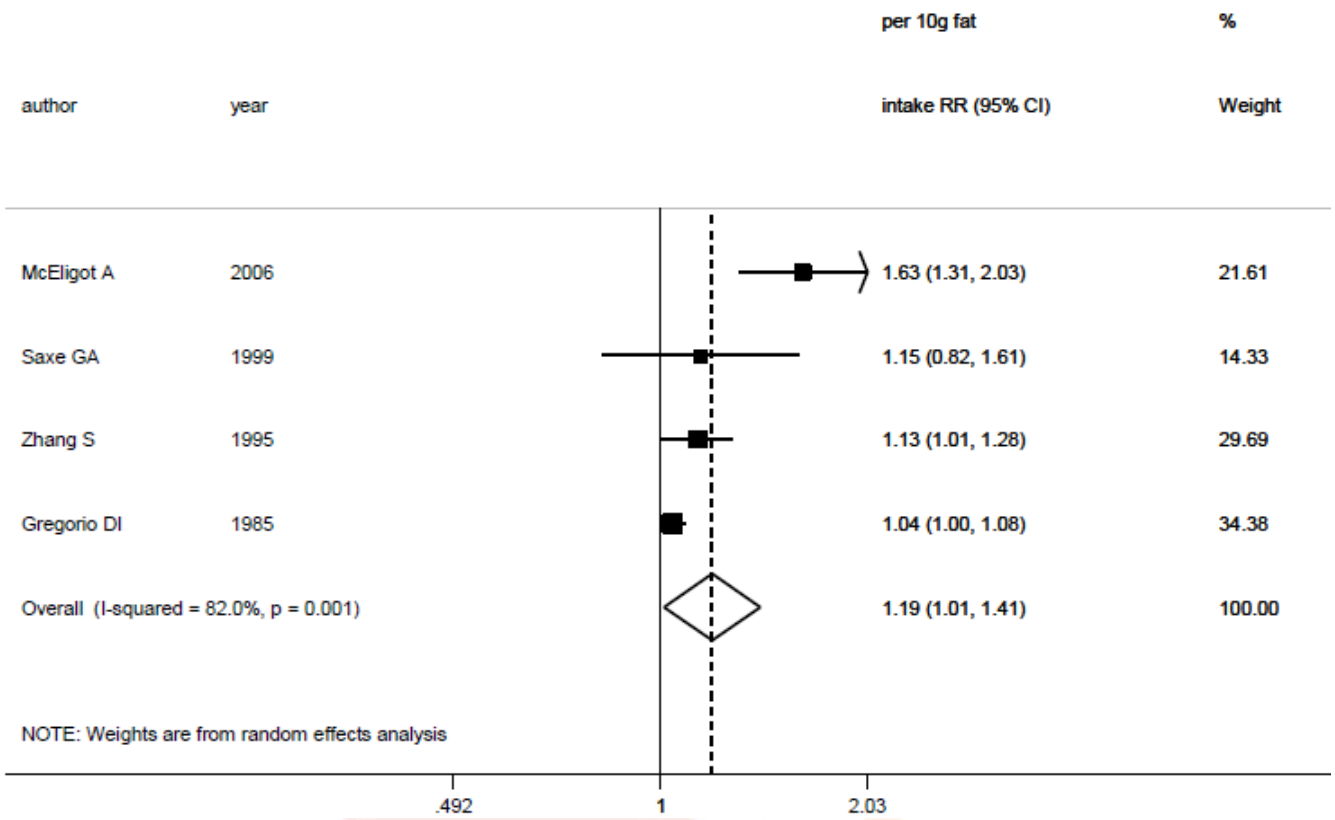
n=794
statistically
significant
9% risk reduction
per 10 g per day




CUP's conclusions: the evidence was sparse but generally consistent

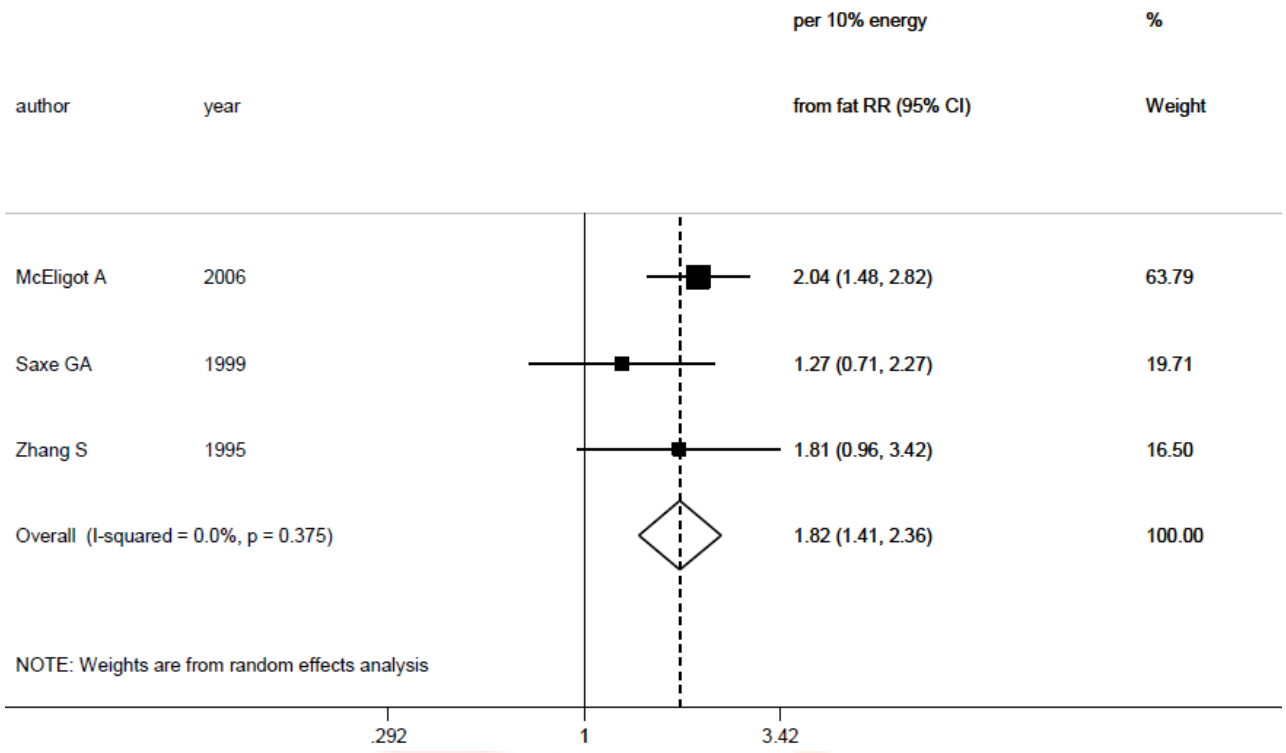
# Total mortality and total fat intake, before

n=178
statistically
significant
19% increased risk
per 10 g per day



# Total mortality and per cent energy intake from fat, before

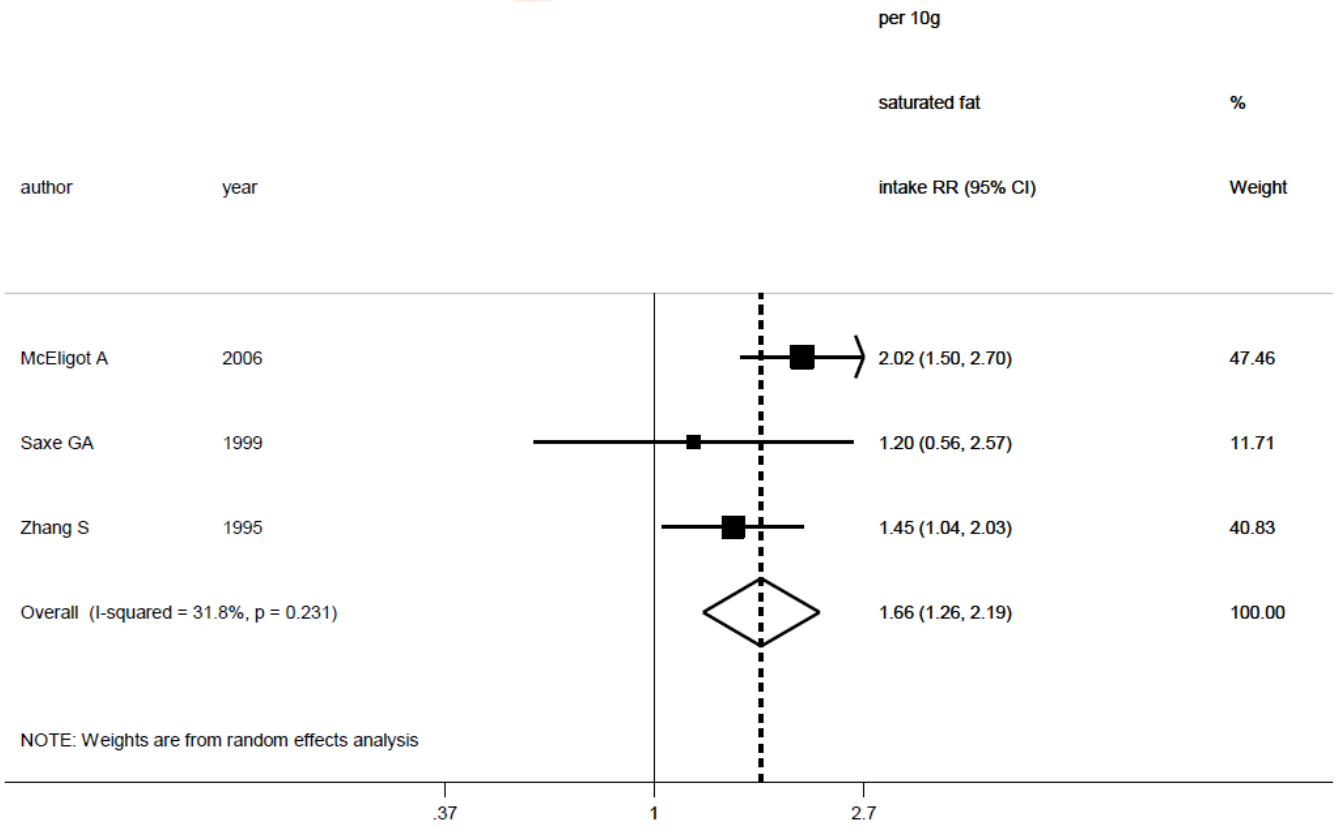
n=178
statistically
significant
82% increased risk
per 10% energy from
fat




CUP's conclusions: the evidence was sparse but generally consistent

# Total mortality and saturated fatty acids, before

n=178
statistically
significant
66% increased risk
per 10g per day




CUP's conclusions: the evidence was sparse but generally consistent

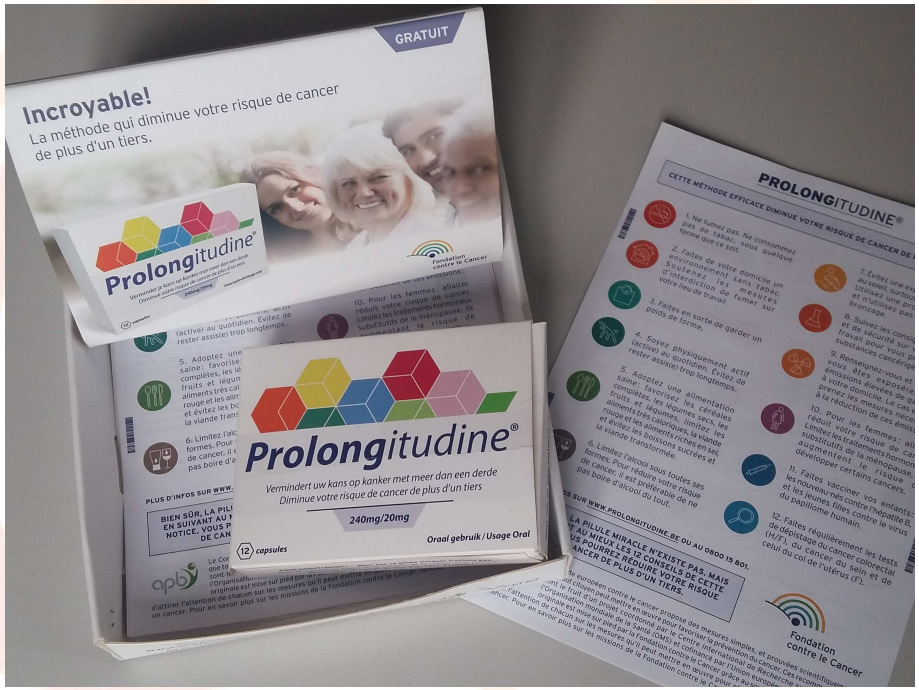
# Recommendations

World Cancer Research Fund International

CUP Continuous Update Project
Analysing research on cancer prevention and survival

1. After treatment for breast cancer our advice, if it fits with the specific medical advice given, is to follow our Cancer Prevention Recommendations (available at wcrf.org), which include eating a healthy diet, being physically active and maintaining a healthy weight.

2. More and better scientific research is needed in order to make specific recommendations for breast cancer survivors.

Le Breast unit dovrebbero prendersi carico di questi aspetti ed inserirli in percorsi integrati di cura

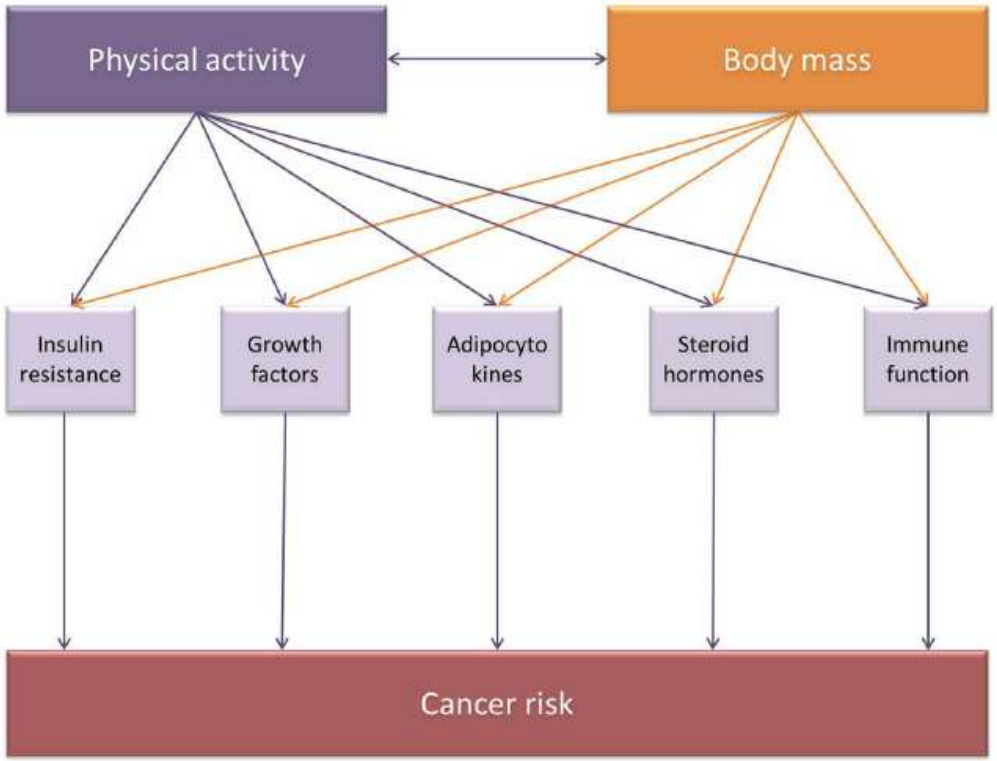



**Fig. 6.** Hypothesized mechanisms linking physical activity to cancer. These include insulin resistance, growth factors, adipocytokines, steroid hormones, and immune function. Physical activity may affect these pathways directly or indirectly by reducing body mass.