Stili di vita e cancro

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Workshop

Dallo screening alla prevenzione primaria:
andata e ritorno
Gli screening e la promozione della salute

Mantova, 29 maggio 2015

Random mutations in healthy cells may explain two-thirds of cancers, like this one in the colon.

Variation in cancer risk among tissues can be explained by the number of stem cell divisions

Cristian Tomasetti[1]* and Bert Vogelstein[2]*

Some tissue types give rise to human cancers millions of times more often than other tissue types. Although this has been recognized for more than a century, it has never been explained. Here, we show that the lifetime risk of cancers of many different types is strongly correlated (0.81) with the total number of divisions of the normal self-renewing cells maintaining that tissue's homeostasis. These results suggest that only a third of the variation in cancer risk among tissues is attributable to environmental factors or inherited predispositions. The majority is due to "bad luck," that is, random mutations arising during DNA replication in normal, noncancerous stem cells. This is important not only for understanding the disease but also for designing strategies to limit the mortality it causes.

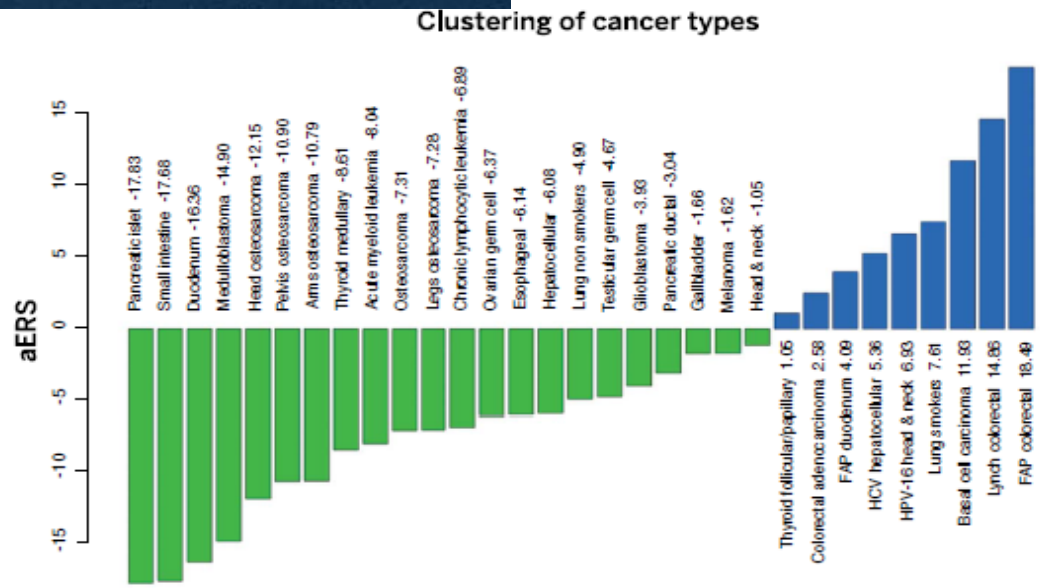


Fig. 2. Stochastic (replicative) factors versus environmental and inherited factors: R-tumor versus D-tumor classification. The adjusted ERS (aERS) is indicated next to the name of each cancer type. R-tumors (green) have negative aERS and appear to be mainly due to stochastic effects associated with DNA replication of the tissues' stem cells, whereas D-tumors (blue) have positive aERS. Importantly, although the aERS was calculated without any knowledge of the influence of environmental or inherited factors, tumors with high aERS proved to be precisely those known to be associated with these factors. For details of the derivation of aERS, see the supplementary materials.

Corrected 23 January 2015; see full text.

International Agency for Research on Cancer

World Health Organization

PRESS RELEASE
N° 231

13 January 2015

Most types of cancer not due to "bad luck"
IARC responds to scientific article claiming that environmental and lifestyle factors account for less than one third of cancers

Lyon, France, 13 January 2015 - The International Agency for Research on Cancer (IARC), the World Health Organization's specialized cancer agency, strongly disagrees with the conclusion of a scientific report[1] on the causes of human cancer published in the journal *Science* on 2 January 2015 by Dr Cristian Tomasetti and Dr Bert Vogelstein.

The study, which has received widespread media coverage, compares the number of lifetime stem cell divisions across a wide range of tissues with lifetime cancer risk and suggests that random mutations (or "bad luck") are "the major contributors to cancer overall, often more important than either hereditary or external environmental factors."

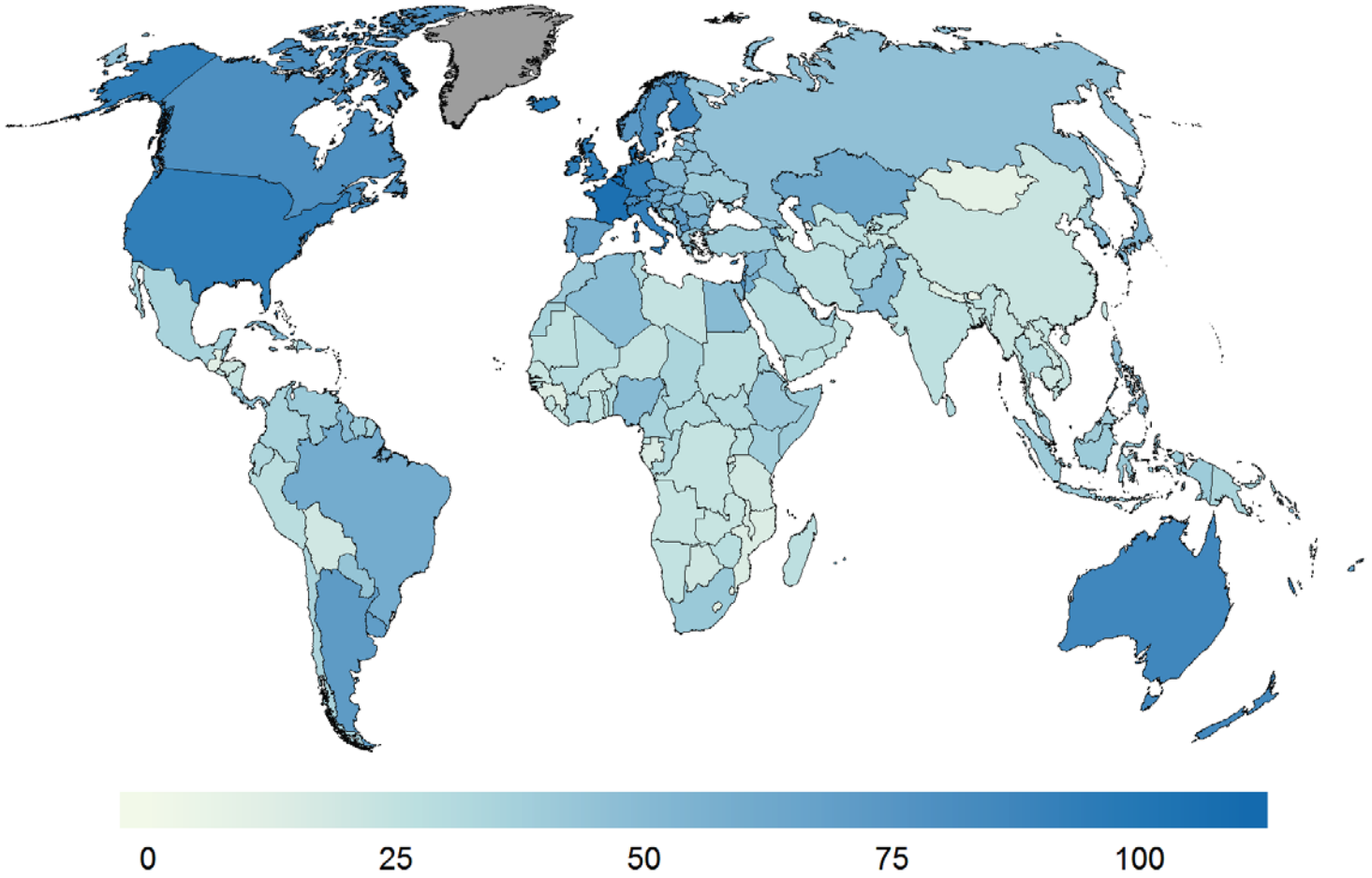
...

Although it has long been clear that the number of cell divisions increases the risk of mutation and, therefore, of cancer, a majority of the most common cancers occurring worldwide are strongly related to environmental and lifestyle exposures. In principle, therefore, these cancers are preventable; based on current knowledge, nearly half of all cancer cases worldwide can be prevented. This is supported in

Estimated Breast Cancer Incidence Worldwide in 2012

GLOBOCAN 2012, International Agency for Research on Cancer

http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx



Estimated age-standardised rates (World) per 100,000

EUROPEAN CODE AGAINST CANCER

12 ways to reduce your cancer risk

Ottobre 2014

1. Do not smoke. Do not use any form of tobacco.
2. Make your home smoke free. Support smoke-free policies in your workplace.
3. Take action to be a healthy body weight.
4. Be physically active in everyday life. Limit the time you spend sitting.
5. Have a healthy diet:
   - Eat plenty of whole grains, pulses, vegetables and fruits.
   - Limit high-calorie foods (foods high in sugar or fat) and avoid sugary drinks.
   - Avoid processed meat; limit red meat and foods high in salt.
6. If you drink alcohol of any type, limit your intake. Not drinking alcohol is better for cancer prevention.
7. Avoid too much sun, especially for children. Use sun protection. Do not use sunbeds.
8. In the workplace, protect yourself against cancer-causing substances by following health and safety instructions.
9. Find out if you are exposed to radiation from naturally high radon levels in your home. Take action to reduce high radon levels.
10. For women:
    - Breastfeeding reduces the mother's cancer risk. If you can, breastfeed your baby.
    - Hormone replacement therapy (HRT) increases the risk of certain cancers. Limit use of HRT.
11. Ensure your children take part in vaccination programmes for:
    - Hepatitis B (for newborns)
    - Human papillomavirus (HPV) (for girls).
12. Take part in organized cancer screening programmes for:
    - Bowel cancer (men and women)
    - Breast cancer (women)
    - Cervical cancer (women).

The European Code Against Cancer focuses on actions that individual citizens can take to help prevent cancer. Successful cancer prevention requires these individual actions to be supported by governmental policies and actions.

Find out more about the European Code Against Cancer at: http://cancer-code-europe.iarc.fr

International Agency for Research on Cancer
World Health Organization

These recommendations are the result of a project coordinated by the International Agency for Research on Cancer and co-financed by the European Commission

Peto & Doll, JNCI 1981	PERCENTUALI DI TUTTE LE MORTI PER TUMORE	
FATTORI	**MIGLIORI STIME**	**RANGE**
Tabacco	**30**	25-40
Alcol	**3**	2-4
Dieta	**35**	10-70
Additivi alimentari	>1	-5-2
Comportamenti riproduttivi e sessuali	4	1-13
Occupazione	2	2-8
Inquinamento	<1	<1-5
Prodotti industriali	1	<1-2
Medicine, procedure mediche	3	0.5-3
Fattori geofisici	10?	2-4
Infezioni	?	1-?
Sconosciuti	?	?

Policy Report 2008

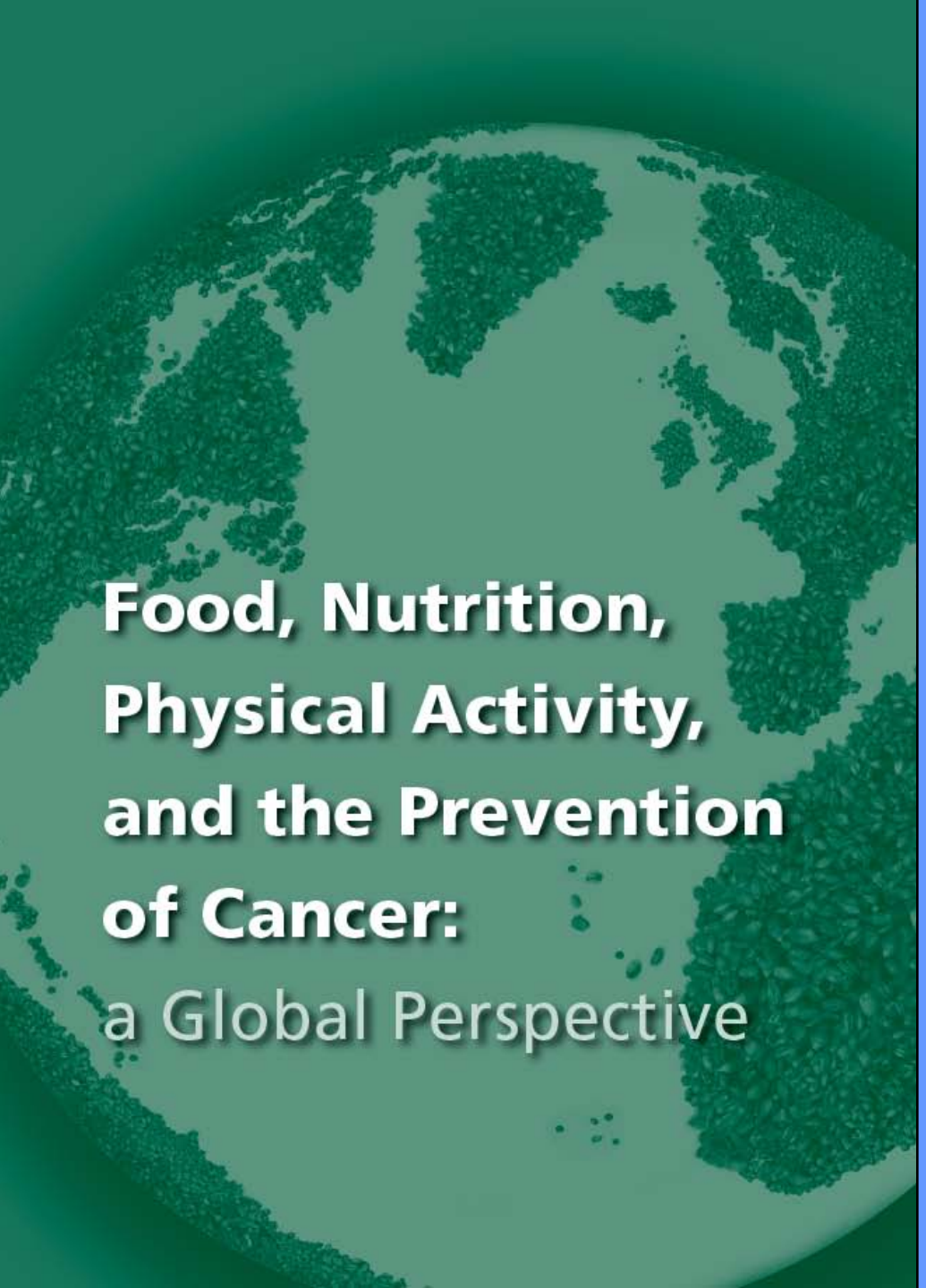
WCRF&AICR

http://www.dietandcancerreport.org/policy_report/index.php

Table 2.1
Estimates[1] of cancer preventability by appropriate food, nutrition, physical activity, and body fatness in four countries[2]

	USA	UK	BRAZIL	CHINA
Mouth, pharynx, larynx	63	67	63	44
Oesophagus	69	75	60	44
Lung	36	33	36	38
Stomach	47	45	41	33
Pancreas	39	41	34	14
Gallbladder	21	16	10	6
Liver	15	17	6	6
Colorectum	45	43	37	17
Breast	38	42	28	20
Endometrium	70	56	52	34
Prostate	11	20	N/A[3]	N/A[3]
Kidney	24	19	13	8
Total for these cancers combined	34	39	30	27
Total for all cancers	24	26	19	20

1. These values are percentages rounded to the nearest whole number and are based on several assumptions. There is a range of likely plausible figures around these point estimates, but they represent the most likely estimates (see appendix A).
2. Based on the conclusions of the 2007 WCRF/AICR Diet and Cancer Report.
3. Exposure data not available



Raccomandazioni per la prevenzione primaria dei tumori

Nov 2007

World Cancer Research Fund

ispo ISTITUTO PER LO STUDIO E LA PREVENZIONE ONCOLOGICA

LE 10 RACCOMANDAZIONI DEL WCRF/AICR
2° Report - 2007

1. Mantieniti magro, nell'intervallo di peso normale.
2. Mantieniti attivo, nell'ambito della tua vita di tutti i giorni.
3. Limita il consumo di alimenti densi di energia ed evita le bevande zuccherate.
4. Consuma preferenzialmente alimenti di origine vegetale.
5. Limita il consumo di carne rossa ed evita le carni conservate.
6. Limita il consumo di bevande alcoliche.
7. Limita il consumo di sale. Evita il consumo di cereali e legumi contaminati da muffe.
8. Assicurati i fabbisogni di nutrienti attraverso la sola dieta
9. Le madri allattino al seno i bambini almeno per i primi sei mesi.
10. Anche per le persone che hanno già avuto un tumore valgono le stesse raccomandazioni.

EPIC

(European Prospective Investigation into Cancer and nutrition)

10 paesi - 500.000 partecipanti

- Tromsø
- Umeå
  Malmö
- Aarhus
  Copenhagen
- Oxford
  Cambridge
- Potsdam
  Heidelberg
- Utrecht
  Bilthoven
- Paris (nationwide)
- Turin
  Varese
  Florence
  Naples
  Ragusa
- Oviedo
  San Sebastian
  Pamplona
  Murcia
  Granada
- Athens

Nei 5 centri italiani: 47.749 volontari (32.578 donne) reclutati 1993 - 1998

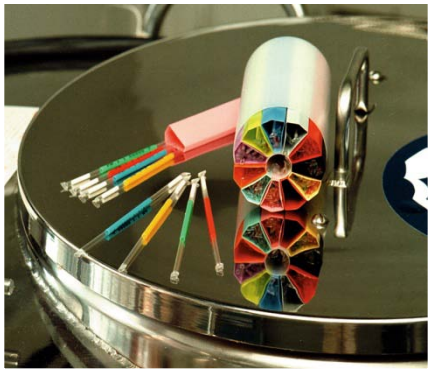
EPIC è uno studio di tipo prospettico: le informazioni (dieta, stile vita,..) sono raccolte al momento dell'arruolamento per tutti i volontari, che vengono poi seguiti nel tempo sino all'identificazione degli eventi sanitari di interesse (ad es.: nuove diagnosi di tumori e malattie cardiovascolari, decessi).

EPIC - Arruolamento 1993-1998 *

PRELIEVO DI SANGUE

30 ml sangue periferico prelevati a ciascun volontario a digiuno aliquotati in :

plasma	**12 straws**
siero	**8 “**
buffy coat	**4 “**
globuli rossi	**4 “**



MISURE ANTROPOMETRICHE

- peso corporeo
- altezza
- altezza da seduto
- circonferenza vita
- circonferenza fianchi
- pressione arteriosa sistolica e diastolica

INFORMAZIONI SULLA DIETA

- Questionario alimentare (FFQ)

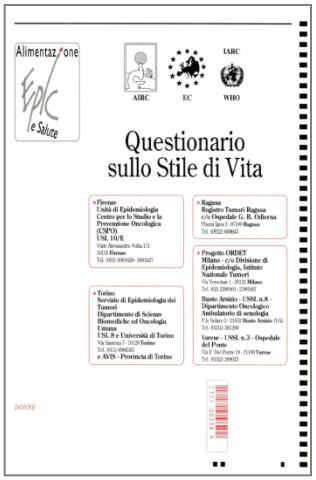
sulla dieta abituale per 521.000 soggetti

- 24h dietary recall

per un campione random corrispondente all’8% dei soggetti EPIC

QUESTIONARIO STILE VITA

- storia riproduttiva
- attività fisica
- abitudime al fumo ed al consumo di alcool
- esposizioni occupazionali
- livello socio-economico



***i partecipanti hanno firmato un consenso informato. EPIC ha avuto la clearance dei CE della IARC e dei centri locali**

IL TUMORE DELLA MAMMELLA

La maggior parte dei fattori conosciuti che modulano il rischio di tumore della mammella (**familiarità, aspetti legati alla storia riproduttiva e personale**) appaiono del tutto o sostanzialmente **non modificabili (a livello individuale)**

- **Età**
- **Storia familiare**
- **Storia personale (*biopsie mammarie*)**
- **Menarca precoce**
- **Menopausa tardiva**
- **Nulliparità**
- **Prima gravidanza tardiva**

La ricerca epidemiologica ha però identificato fattori legati ad alimentazione e allo stile di vita che appaiono potenzialmente modificabili, rendendo quindi possibili interventi di prevenzione primaria anche per questo tumore.

- **Sovrappeso ed obesità in post menopausa**
- **Sedentarietà**
- **Consumo di bevande alcoliche**
- **Alimentazione** ***(diete ricche di grassi animali, a elevato carico glicemico, a basso consumo di verdure e fibre)***
- **Fumo (attivo e passivo)**

Obesità e tumore della mammella

- **Numerosi studi dimostrano che l'obesità aumenta il rischio nelle donne in post menopausa.**

- **Uno dei meccanismi proposti è quello secondo cui nelle donne obese sarebbero più alti i livelli di estrogeni endogeni. Il tessuto adiposo è infatti implicato nella produzione degli estrogeni a partire dagli androgeni surrenalici attraverso l'enzima aromatasi.**

- **Al contrario l'obesità nelle donne in pre-menopausa è stata associata con un rischio ridotto di CaM prima della menopausa, il meccanismo è ancora poco chiaro ma probabilmente coinvolge aspetti ormonali.**

Int. J. Cancer: **111**, 762–771 (2004)

Publication of the International Union Against Cancer

BODY SIZE AND BREAST CANCER RISK: FINDINGS FROM THE EUROPEAN PROSPECTIVE INVESTIGATION INTO CANCER AND NUTRITION (EPIC)

Petra H. LAHMANN[1]*, Kurt HOFFMANN[1], Naomi ALLEN[2], Carla H. VAN GILS[3], Kay-Tee KHAW[4], Bertrand TEHARD[5], Franco BERRINO[6], Anne TJØNNELAND[7], Janne BIGAARD[7], Anja OLSEN[7], Kim OVERVAD[8], Françoise CLAVEL-CHAPELON[5], Gabriele NAGEL[9], Heiner BOEING[1], Dimitrios TRICHOPOULOS[10], George ECONOMOU[11], George BELLOS[12], Domenico PALLI[13], Rosario TUMINO[14], Salvatore PANICO[15], Carlotta SACERDOTE[16], Vittorio KROGH[6], Petra H.M. PEETERS[3], H. Bas BUENO-DE-MESQUITA[17], Eiliv LUND[18], Eva ARDANAZ[19], Pilar AMIANO[20], Guillem PERA[21], José R. QUIRÓS[22], Carmen MARTÍNEZ[23], María J. TORMO[24], Elisabet WIRFÄLT[25], Göran BERGLUND[25], Göran HALLMANS[26], Timothy J. KEY[2], Gillian REEVES[2], Sheila BINGHAM[27], Teresa NORAT[28], Carine BIESSY[28], Rudolf KAAKS[28] and Elio RIBOLI[28]

The evidence for anthropometric factors influencing breast cancer risk is accumulating, but uncertainties remain concerning the role of fat distribution and potential effect modifiers. We used data from 73,542 premenopausal and 103,344 postmenopausal women from 9 European countries, taking part in the EPIC study. RRs from Cox regression models were calculated, using measured height, weight, BMI and waist and hip circumferences; categorized by cohort-wide quintiles; and expressed as continuous variables, adjusted for study center, age and other risk factors. During 4.7 years of follow-up, 1,879 incident invasive breast cancers were identified. In postmenopausal women, current HRT modified the body size–breast cancer association. Among nonusers, weight, BMI and hip circumference were positively associated with breast cancer risk (all $p_{trend} \leq 0.002$); obese women (BMI > 30) had a 31% excess risk compared to women with BMI < 25. Among HRT users, body measures were inversely but nonsignificantly associated with breast cancer. Excess breast cancer risk with HRT was particularly evident among lean women. Pooled RRs per height increment of 5 cm were 1.05 (95% CI 1.00–1.16) in premenopausal and 1.10 (95% CI 1.05–1.16) in postmenopausal women. Among premenopausal women, hip circumference was the only other measure significantly related to breast cancer ($p_{trend} = 0.03$), after accounting for BMI. In postmenopausal women not taking exogenous hormones, general obesity is a significant predictor of breast cancer, while abdominal fat assessed as waist–hip ratio or waist circumference was not related to excess risk when adjusted for BMI. Among premenopausal women, weight and BMI showed nonsignificant inverse associations with breast cancer.

Int. J. Cancer: **118,** 2832–2839 (2006)

Anthropometric measures, endogenous sex steroids and breast cancer risk in postmenopausal women: A study within the EPIC cohort

Sabina Rinaldi[1], Tim J Key[2], Petra H.M. Peeters[3], Petra H. Lahmann[4], Annekatrin Lukanova[5], Laure Dossus[1], Carine Biessy[1], Paolo Vineis[6,7], Carlotta Sacerdote[6], Franco Berrino[8], Salvatore Panico[9], Rosario Tumino[10], Domenico Palli[11], Gabriele Nagel[12], Jakob Linseisen[12], Heiner Boeing[4], Andrew Roddam[2], Sheila Bingham[13], Kay-Tee Khaw[14], John Chloptios[15], Antonia Trichopoulou[15], Dimitrios Trichopoulos[15], Bertrand Tehard[16], Francoise Clavel-Chapelon[16], Carlos A. Gonzalez[17], Nerea Larrañaga[18], Aurelio Barricarte[19], J. Ramón Quirós[20], Maria-Dolores Chirlaque[21], Carmen Martinez[22], Evelyne Monninkhof[3], Diederick E. Grobbee[3], H. Bas Bueno-de-Mesquita[23], Pietro Ferrari[1], Nadia Slimani[1], Elio Riboli[1] and Rudolf Kaaks[1]*

TABLE III – GEOMETRIC MEANS (95% CI) OF SEX HORMONES BY ANTHROPOMETRIC MEASURES IN 1,139 HEALTHY POSTMENOPAUSAL WOMEN, ADJUSTED FOR AGE AND LABORATORY BATCH

Anthropometry	*N*	T (nmol/l)	fT (pmol/l)	Δ_4 (nmol/l)	DHEAS (μmol/l)	E_2 (pmol/l)	fE_2 (pmol/l)	E_1 (pmol/l)	SHBG (nmol/l)
BMI									
<23.0	227	1.10 (1.02–1.18)	15.1 (13.9–16.4)	2.87 (2.65–3.09)	1.88 (1.73–2.05)	81.8 (77.7–86.1)	1.94 (1.83–2.05)	131.2 (125.0–137.6)	44.5 (41.5–47.7)
23.0–25.0	230	1.13 (1.06–1.22)	17.4 (16.0–18.8)	2.92 (2.70–3.14)	1.96 (1.80–2.13)	82.1 (78.0–86.4)	2.06 (1.95–2.18)	134.4 (128.2–140.9)	38.3 (35.7–41.0)
25.1–27.1	226	1.14 (1.06–1.22)	18.5 (17.0–20.1)	3.06 (2.83–3.30)	1.88 (1.73–2.05)	87.3 (82.9–92.0)	2.27 (2.14–2.40)	142.1 (135.4–149.0)	34.5 (32.2–37.0)
27.2–30.2	228	1.17 (1.09–1.26)	20.6 (19.0–22.4)	3.17 (2.93–3.42)	2.02 (1.85–2.19)	92.8 (88.1–97.7)	2.51 (2.38–2.66)	148.3 (141.4–155.5)	29.6 (27.6–31.7)
>30.2	228	1.23 (1.14–1.32)	23.8 (21.9–25.9)	3.07 (2.84–3.32)	1.93 (1.77–2.11)	105.2 (99.8–110.9)	3.01 (2.84–3.20)	165.1 (157.3–173.5)	24.3 (22.6–26.1)
p for trend		0.04	<0.0001	0.08	0.57	<0.0001	<0.0001	<0.0001	<0.0001

T=testosterone;Δ_4= androstenedione; DHEAS=deidroepiandrosterone-solfato; E_2=estradiolo; E_1= estrone SHBG= globuline leganti gli steroidi sessuali

Body weight and incidence of breast cancer defined by estrogen and progesterone receptor status—A meta-analysis

Reiko Suzuki[1,2,3], Nicola Orsini[1], Shigehira Saji[4], Timothy J. Key[2] and Alicja Wolk[1*]

Int. J. Cancer: **124,** 698–712 (2009)

Epidemiological evidence indicates that the association between body weight and breast cancer risk may differ across menopausal status as well as the estrogen receptor (ER) and progesterone receptor (PR) tumor status. To date, no meta-analysis has been conducted to assess the association between body weight and ER/PR defined breast cancer risk, taking into account menopausal status and study design. We searched MEDLINE for relevant studies published from January 1, 1970 through December 31, 2007. Summarized risk estimates with 95% confidence intervals (CIs) were calculated using a random-effects model. The summarized results of 9 cohorts and 22 case-control studies comparing the highest versus the reference categories of relative body weight showed that the risk for ER+PR+ tumors was 20% lower (95% CI = −30% to −8%) among premenopausal (2,643 cases) and 82% higher (95% CI = 55–114%) among postmenopausal (5,469 cases) women. The dose-response meta-analysis of ER+PR+ tumors showed that each 5-unit increase in body mass index (BMI, kg/m^2) was associated with a 33% increased risk among postmenopausal women (95% CI = 20–48%) and 10% decreased risk among premenopausal women (95% CI = −18% to −1%). No associations were observed for ER−PR− or ER+PR− tumors. For discordant tumors ER+PR− (pre) and ER−PR+ (pre/post) the number of cases were too small (<200) to interpret results. The relation between body weight and breast cancer risk is critically dependent on the tumor's ER/PR status and the woman's menopausal status. Body weight control is the effective strategy for preventing ER+PR+ tumors after menopause.

Weight change in middle adulthood and breast cancer risk in the EPIC-PANACEA study

Marleen J. Emaus[1], Carla H. van Gils[1], Marije F. Bakker[1], Charlotte N. Steins Bisschop[1], Evelyn M. Monninkhof[1], H. Bas Bueno-de-Mesquita[2,3,4], Noémie Travier[5], Tina Landsvig Berentzen[6], Kim Overvad[7], Anne Tjønneland[8], Isabelle Romieu[9], Sabina Rinaldi[9], Veronique Chajes[9], Marc J. Gunter[4], Françoise Clavel-Chapelon[10,11,12], Guy Fagherazzi[10,11,12], Sylvie Mesrine[10,11,12], Jenny Chang-Claude[13], Rudolf Kaaks[13], Heiner Boeing[14], Krasimira Aleksandrova[14], Antonia Trichopoulou[15,16], Androniki Naska[15,16], Philippos Orfanos[15,16], Domenico Palli[17], Claudia Agnoli[18], Rosario Tumino[19], Paolo Vineis[4,20], Amalia Mattiello[21], Tonje Braaten[22], Kristin Benjaminsen Borch[22], Eiliv Lund[22], Virginia Menéndez[23], María-José Sánchez[24,25], Carmen Navarro[25,26,27], Aurelio Barricarte[25,28], Pilar Amiano[29], Malin Sund[30], Anne Andersson[31], Signe Borgquist[32,33], Åsa Olsson[34], Kay-Tee Khaw[35], Nick Wareham[35,36], Ruth C. Travis[37], Elio Riboli[4], Petra H.M. Peeters[1,4] and Anne M. May[1]

Long-term weight gain (*i.e.*, weight gain since age 20) has been related to higher risk of postmenopausal breast cancer, but a lower risk of premenopausal breast cancer. The effect of weight change in middle adulthood is unclear. We investigated the association between weight change in middle adulthood (*i.e.*, women aged 40–50 years) and the risk of breast cancer before and after the age of 50. We included female participants of the European Prospective Investigation into Cancer and Nutrition cohort, with information on anthropometric measures at recruitment and after a median follow-up of 4.3 years. Annual weight change was categorized using quintiles taking quintile 2 and 3 as the reference category (−0.44 to 0.36 kg/year). Multivariable Cox proportional hazards regression analysis was used to examine the association. 205,723 women were included and 4,663 incident breast cancer cases were diagnosed during a median follow-up of 7.5 years (from second weight assessment onward). High weight gain (Q5: 0.83–4.98 kg/year) was related to a slightly, but significantly higher breast cancer risk ($HR_{Q5\_versus\_Q2/3}$: 1.09, 95% CI: 1.01−1.18). The association was more pronounced for breast cancer diagnosed before or at age 50 ($HR_{Q5\_versus\_Q2/3}$: 1.37, 95% CI: 1.02−1.85). Weight loss was not associated with breast cancer risk. There was no evidence for heterogeneity by hormone receptor status. In conclusion, high weight gain in middle adulthood increases the risk of breast cancer. The association seems to be more pronounced for breast cancer diagnosed before or at age 50. Our results illustrate the importance of avoiding weight gain in middle adulthood.

Int J Cancer on line April 2014

Meccanismi ipotizzati per l'associazione fra tumore della mammella e obesità

❖ Più **alti livelli di estrogeni** endogeni nelle donne in post-menopausa obese

(Il tessuto adiposo è infatti implicato nella produzione degli estrogeni a partire dagli androgeni surrenalici attraverso l'enzima aromatasi.)

❖L'obesità influenza il livello di **numerosi ormoni e fattori di crescita. l'insulino-resistenza** è associata ad **obesità addominale**

IGF1 e insulina sono elevate nei soggetti obesi e possono promuovere la crescita di cellule neoplastiche.

❖ Produzione da parte degli adipociti di **fattori pro-infiammatori e di crescita** (IL-6, TNF-alpha, leptina,…)

Attività fisica e tumore della mammella

☞A partire dagli anni ’90, **numerosi studi epidemiologici** hanno fornito evidenze coerenti che una **attività fisica regolare** ha un **effetto protettivo** nei confronti di alcuni tra i tumori più frequenti tra i quali il tumore della **mammella**

☞ è stata evidenziata una **relazione dose-risposta** con la durata delle sessioni di attività fisica, la loro intensità e la continuità negli anni

Attività fisica e tumore della mammella

Il Fondo Internazionale per la Ricerca sul Cancro nel Rapporto 2007 " Food, Nutrition, Physical Activity and the Prevention of Cancer" ha classificato come ***"probabile"*** l'evidenza dell'associazione inversa tra attività fisica e tumore mammario in post-menopausa, mentre in pre-menopausa l'evidenza è stata classificata come "***limitata***"

- In media (in 73 studi,di cui 33 di coorte.pubblicati al dicembre 2009) è stata evidenziata una riduzione di rischio intorno al 25% nelle donne più attive rispetto alle inattive. Le associazioni appaiono più forti per le attività condotte nel tempo libero, con regolarità e nelle donne in menopausa *(Lynch BM et al Recent Results Cancer Res 2011)*

Attività fisica e tumore della mammella

Metanalisi di 31 studi prospettici

Table 2 Pooled measures on the relation of physical activity to breast cancer

	Random effect model	Fixed effect model	I^2 (%)	Number of studies	Number of breast cancer cases
Overall	0.87 (0.83–0.92)	0.88 (0.85–0.91)	29.5	31	63,786
Age-adjusted RR	0.85 (0.79–0.90)	0.88 (0.85–0.91)	54.3	18	29,321
RR with BMI unadjusted	0.90 (0.85–0.96)	0.89 (0.85–0.93)	35.5	14	34,664
RR with BMI adjusted	0.87 (0.83–0.91)	0.88 (0.85–0.91)	23.0	23	42,779
Menopausal status					
Premenopausal	0.77 (0.69–0.86)	0.77 (0.72–0.84)	14.5	6	2,258
Postmenopausal	0.87 (0.87–0.92)	0.88 (0.84–0.92)	18.2	17	32,623
Body mass index (BMI)					
<25 kg/m^2	0.72 (0.65–0.81)	0.72 (0.65–0.81)	0.00	9	4,365
>25 kg/m^2	0.93 (0.83–1.05)	0.93 (0.83–1.05)	0.00	8	3,857

Wu Y et al Breast Cancer Res Treat 2012

Riduzione del rischio di sviluppare un tumore mammario all'aumentare del livello di attività fisica **sia in post- che in pre- menopausa**, per i diversi tipi di attività e in diverse fasi della vita

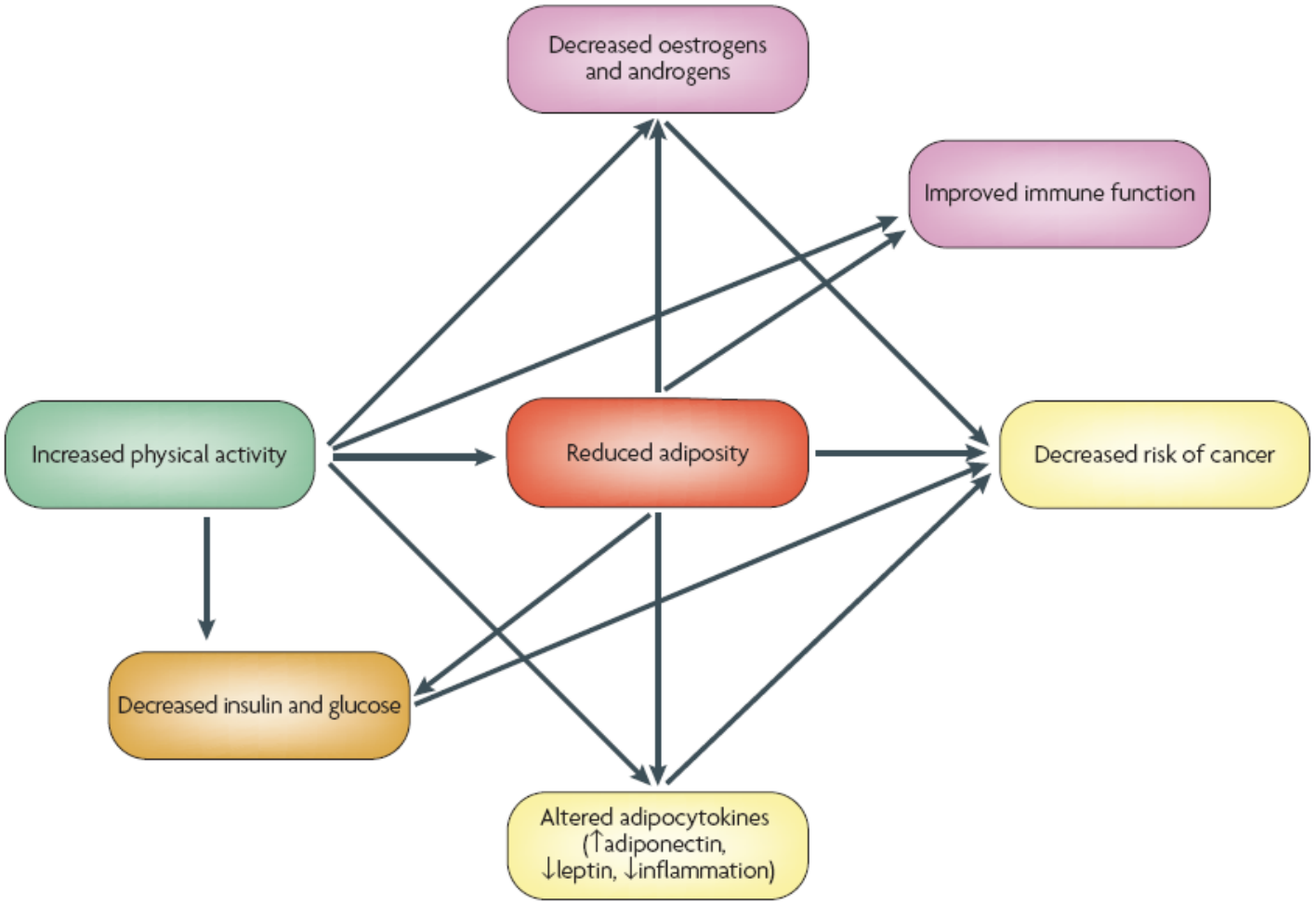


Figure 1 | **Hypothesized mechanisms linking physical activity to cancer risk or prognosis.** Physical activity might work through reducing the amount of adipose tissue, which lowers production of sex hormones, insulin, leptin and inflammatory markers, thereby decreasing the exposure to these potentially carcinogenic hormones and peptides and reducing cancer risk.

Mc Tiernan A. Mechanisms linking physical activity with cancer. Nat. Rev Cancer 2008; 8:205-11

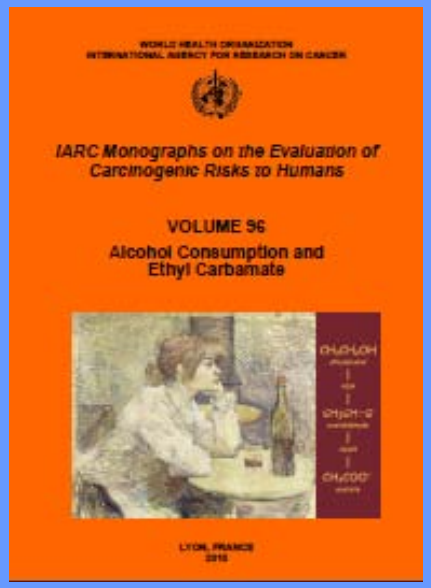
ALCOL e TUMORI

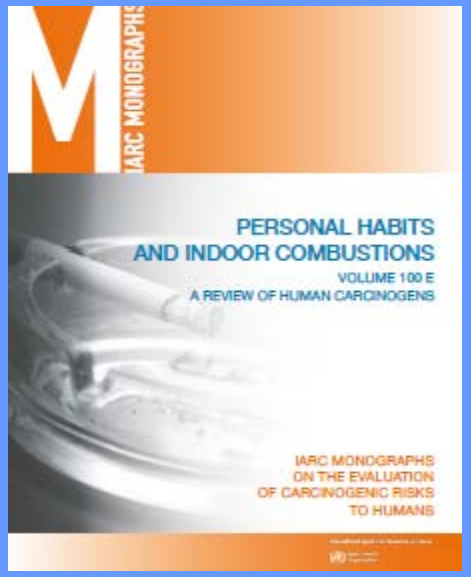
- **Bevande alcoliche**

→ **Cancerogeni (Gruppo I)**

- **Etanolo**

Cavità orale
Faringe
Laringe
Esofago
Tumore primitivo del fegato
Mammella
Colon-retto





IARC Monographs on the Evaluation of Carcinogenic Risks to Humans.
Volume 96 (2010) e volume 100E (2012)

Alcuni meccanismi proposti:

- L'acetaldeide, il metabolita principale dell'etanolo, è un noto cancerogeno e mutageno
- Induzione di alcuni sistemi enzimatici (Fase 1) attivazione di procancerogeni
- Deficit nutrizionali a carico ad es. dei folati e di altri micronutrienti
- Azione di solvente nei confronti di altri cancerogeni
- Alterazioni del sistema immunitario
- Effetto sui livelli di ormoni sessuali

•Consumo di bevande alcoliche e tumore mammario

•Numerosi studi epidemiologici hanno evidenziato un'associazione positiva tra consumo di bevande alcoliche e rischio di tumore della mammella.

- **Il tipo di bevanda alcolica non sembra influenzare il rischio.**
- **Il rischio aumenta linearmente in maniera dose-dipendente:** ogni aumento nel consumo di 10 g corrisponde ad un aumento di rischio tra il 7-9% e il 3%.
  (*Smith Warner et al, JAMA 1998; Hamajima Br J Cancer 2002; EPIC - Tjønneland et al, 2007)*
- Una metanalisi basata su studi prospettici (4) e caso-controllo (16) nei quali era disponibile l'informazione sui recettori ormonali dei tumori ha evidenziato rischi analoghi per tutti i sottotipi esclusi gli ER- / PR-.
  (Suzuki R et al Int J Cancer 2008)

Alcohol intake and breast cancer in the European Prospective investigation into Cancer and Nutrition

Romieu I, Scoccianti C, Chajes V, de Batlle J, Biessy C, Dossus L, Baglietto L, Clavel-Chapelon F, Overvad K, Olsen A, Tjønneland A, Kaaks R, Lukanova A, Boeing H, Trichopoulou A, Lagiou P, Trichopoulos D, Palli D, Sieri S, Tumino R, Vineis P, Panico S, Bueno-de-Mesquita HB, Gils CH, Peeters P, Lund E, Skeie G, Weiderpass E, Quirós JR, Chirlaque MD, Ardanaz E, Sánchez MJ, Duell EJ, Amiano P, Borgquist S, Girfalco E, Hallmans G, Johansson I, Nilsson LM, Khaw KT, Wareham N, Key TJ, Travis RC, Murphy N, Wark PA, Ferrari P, Riboli E. **Int J Cancer. 2015 Feb 9. doi: 10.1002/ijc.29469. [Epub ahead of print]**

Alcohol intake has been associated to breast cancer in pre and postmenopausal women; however results are inconclusive regarding tumor hormonal receptor status, and potential modifying factors like age at start drinking. Therefore, we investigated the relation between alcohol intake and the risk of breast cancer using prospective observational data from the European Prospective Investigation into Cancer and Nutrition (EPIC). Up to 334,850 women, aged 35-70 years at baseline, were recruited in ten European countries and followed up an average of 11 years. Alcohol intake at baseline and average lifetime alcohol intake were calculated from country-specific dietary and lifestyle questionnaires. The study outcomes were the Hazard ratios (HR) of developing breast cancer according to hormonal receptor status. During 3,670,439 person-years, 11,576 incident breast cancer cases were diagnosed. Alcohol intake was significantly related to breast cancer risk, **for each 10g/day increase in alcohol intake the HR increased by 4.2% (95% CI: 2.7%-5.8%).** Taking 0 to 5g/day as reference, alcohol intake of >5 to 15g/day was related to a 5.9% increase in breast cancer risk (95% CI: 1%-11%). Significant increasing trends were observed between alcohol intake and ER+/PR+, ER-/PR-, HER2- and ER-/PR-/HER2- tumors. Breast cancer risk was stronger among women who started drinking prior to first full-time pregnancy Overall, our results confirm the association between alcohol intake and both hormone receptor positive and hormone receptor negative breast tumors, suggesting that timing of exposure to alcohol drinking may affect the risk. Therefore, women should be advised to control their alcohol consumption.

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Active and passive cigarette smoking and breast cancer risk: Results from the EPIC cohort

Laure Dossus[1,2], Marie-Christine Boutron-Ruault[1,2], Rudolf Kaaks[3], Inger T. Gram[4,5], Alice Vilier[1,2], Béatrice Fervers[6], Jonas Manjer[7], Anne Tjonneland[8], Anja Olsen[8], Kim Overvad[9], Jenny Chang-Claude[3], Heiner Boeing[10], Annika Steffen[10], Antonia Trichopoulou[11,12], Pagona Lagiou[11,13,14], Maria Sarantopoulou[11,12], Domenico Palli[15], Franco Berrino[16], Rosario Tumino[17], Paolo Vineis[18,19], Amalia Mattiello[20], H. Bas Bueno-de-Mesquita[21,22], Franzel J.B. van Duijnhoven[21,23], Marieke F. Bakker[24], Petra HM Peeters[24,25], Elisabete Weiderpass[4,26,27,28], Eivind Bjerkaas[4], Tonje Braaten[4], Virginia Menéndez[29], Antonio Agudo[30], Maria-Jose Sanchez[31,32], Pilar Amiano[32,33], Maria-Jose Tormo[32,34], Aurelio Barricarte[32,35], Salma Butt[36], Kay-Tee Khaw[37], Nicholas Wareham[38], Tim J. Key[39], Ruth C. Travis[39], Sabina Rinaldi[40], Valerie McCormack[41], Isabelle Romieu[40], David G. Cox[42], Teresa Norat[42], Elio Riboli[42] and Françoise Clavel-Chapelon[1,2]

Recent cohort studies suggest that increased breast cancer risks were associated with longer smoking duration, higher pack-years and a dose-response relationship with increasing pack-years of smoking between menarche and first full-term pregnancy (FFTP). Studies with comprehensive quantitative life-time measures of passive smoking suggest an association between passive smoking dose and breast cancer risk. We conducted a study within the European Prospective Investigation into Cancer and Nutrition to examine the association between passive and active smoking and risk of invasive breast cancer and possible effect modification by known breast cancer risk factors. Among the 322,988 women eligible for the study, 9,822 developed breast cancer (183,608 women with passive smoking information including 6,264 cases). When compared to women who never smoked and were not being exposed to passive smoking at home or work at the time of study registration, current, former and currently exposed passive smokers were at increased risk of breast cancer (hazard ratios (HR) [95% confidence interval (CI)] 1.16 [1.05–1.28], 1.14 [1.04–1.25] and 1.10 [1.01–1.20], respectively). Analyses exploring associations in different periods of life showed the most important increase in risk with pack-years from menarche to FFTP (1.73 [1.29–2.32] for every increase of 20 pack-years) while pack-years smoked after menopause were associated with a significant decrease in breast cancer risk (HR = 0.53, 95% CI: 0.34–0.82 for every increase of 20 pack-years). Our results provide an important replication, in the largest cohort to date, that smoking (passively or actively) increases breast cancer risk and that smoking between menarche and FFTP is particularly deleterious.

Alimentazione e t. mammella

Consumption of Vegetables and Fruits and Risk of Breast Cancer

Carla H. van Gils, PhD
Petra H. M. Peeters, MD, PhD
H. Bas Bueno-de-Mesquita, MD, MPH, PhD
Hendriek C. Boshuizen, PhD
Petra H. Lahmann, PhD
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Domenico Palli, MD
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Salvatore Panico, MD, MSc
Paolo Vineis, MD
Carlos A. Gonzalez, MD, MPH, PhD
Eva Ardanaz, PhD
Maria-José Sánchez, MD, PhD
Pilar Amiano, MS
Carmen Navarro, MD, PhD, MSc
José R. Quirós, MD
Timothy J. Key, DPhil
Naomi Allen, DPhil
Kay-Tee Khaw, MBBChir, FRCP
Sheila A. Bingham, PhD
Theodora Psaltopoulou, MD
Maria Koliva, PhN
Antonia Trichopoulou, MD
Gabriële Nagel, MPH
Jakob Linseisen, PhD
Heiner Boeing, PhD
Göran Berglund, MD, PhD
Elisabet Wirfält, MPH, PhD
Göran Hallmans, MD, PhD
Per Lenner, MD, PhD
Kim Overvad, MD, PhD
Anne Tjønneland, MD, PhD
Anja Olsen, PhD, MSc
Eiliv Lund, MD, PhD
Dagrun Engeset, MSc
Elin Alsaker, MSc
Teresa Norat, PhD
Rudolf Kaaks, PhD
Nadia Slimani, MSc, PhD
Elio Riboli, MD, M

Context The intake of vegetables and fruits has been thought to protect against breast cancer. Most of the evidence comes from case-control studies, but a recent pooled analysis of the relatively few published cohort studies suggests no significantly reduced breast cancer risk is associated with vegetable and fruit consumption.

Objective To examine the relation between total and specific vegetable and fruit intake and the incidence of breast cancer.

Design, Setting, and Participants Prospective study of 285526 women between the ages of 25 and 70 years, participating in the European Prospective Investigation Into Cancer and Nutrition (EPIC) study, recruited from 8 of the 10 participating European countries. Participants completed a dietary questionnaire in 1992-1998 and were followed up for incidence of cancer until 2002.

Main Outcome Measures Relative risks for breast cancer by total and specific vegetable and fruit intake. Analyses were stratified by age at recruitment and study center. Relative risks were adjusted for established breast cancer risk factors.

Results During 1486402 person-years (median duration of follow-up, 5.4 years), 3659 invasive incident breast cancer cases were reported. No significant associations between vegetable or fruit intake and breast cancer risk were observed. Relative risks for the highest vs the lowest quintile were 0.98 (95% confidence interval [CI], 0.84-1.14) for total vegetables, 1.09 (95% CI, 0.94-1.25) for total fruit, and 1.05 (95% CI, 0.92-1.20) for fruit and vegetable juices. For 6 specific vegetable subgroups no associations with breast cancer risk were observed either.

Conclusion Although the period of follow-up is limited for now, the results suggest that total or specific vegetable and fruit intake is not associated with risk for breast cancer.

JAMA. 2005;293:183-193

www.jama.com

Fruit and vegetables consumption and breast cancer risk: the EPIC Italy study

Giovanna Masala · Melania Assedi · Benedetta Bendinelli · Ilaria Ermini · Sabina Sieri · Sara Grioni · Carlotta Sacerdote · Fulvio Ricceri · Salvatore Panico · Amalia Mattiello · Rosario Tumino · Maria Concetta Giurdanella · Franco Berrino · Calogero Saieva · Domenico Palli

Breast Cancer Res Treat (2012) 132:1127–1136

Abstract The role of fruit and vegetables in breast cancer (BC) development has long been debated. A large variety of vegetables and fruit are consumed by Mediterranean populations, a favourable setting for evaluating the effects of these foods. The association between vegetables and fruit consumption, overall and by specific types, and BC risk was studied in the Italian section of the European Prospective Investigation into Cancer and Nutrition study. Over 31,000 women, aged 36-64 years, recruited in five Italian centers between 1993 and 1998, were available for analyses with dietary and lifestyle information and anthropometric measurements. After a median follow-up of 11.25 years, 1,072 invasive and in situ incident BC cases were identified. Cox proportional hazard models (adjusted for education, anthropometry, reproductive history, hormone replacement therapy, physical activity, alcohol consumption and smoking habits) showed an inverse association between consumption of all vegetables and BC risk (highest vs. lowest quintile HR 0.65; 95% CI 0.53–0.81, P for trend = 0.003). According to subtypes of vegetables, an inverse association emerged for increasing consumption of leafy vegetables (highest vs. lowest quintile HR 0.70; 95% CI 0.57–0.86, P for trend = 0.0001) and fruiting vegetables (highest vs. lowest quintile HR 0.75; 95% CI 0.60–0.94, P for trend = 0.01). An inverse association also emerged with increasing consumption of raw tomatoes (P for trend = 0.03). In contrast, no association of fruit, overall or by subtypes, with BC risk was found. In this Mediterranean population, a clear protective role of increasing vegetables consumption, mainly leafy and fruiting vegetables, on BC risk emerged.

Dietary fiber intake and risk of hormonal receptor–defined breast cancer in the European Prospective Investigation into Cancer and Nutrition study[1–3]

Pietro Ferrari, Sabina Rinaldi, Mazda Jenab, Annekatrin Lukanova, Anja Olsen, Anne Tjønneland, Kim Overvad, Françoise Clavel-Chapelon, Guy Fagherazzi, Marina Touillaud, Rudolf Kaaks, Anne von Rüsten, Heiner Boeing, Antonia Trichopoulou, Pagona Lagiou, Vassiliki Benetou, Sara Grioni, Salvatore Panico, Giovanna Masala, Rosario Tumino, Silvia Polidoro, Marije F Bakker, Carla H van Gils, Martine M Ros, H Bas Bueno-de-Mesquita, Sanda Krum-Hansen, Dagrun Engeset, Guri Skeie, Amiano Pilar, Maria-José Sánchez, Genevieve Buckland, Eva Ardanaz, Dolores Chirlaque, Laudina Rodriguez, Ruth Travis, Tim Key, Kay-Tee Khaw, Nicholas J Wareham, Malin Sund, Per Lenner, Nadia Slimani, Teresa Norat, Dagfinn Aune, Elio Riboli, and Isabelle Romieu

Background: Limited scientific evidence has characterized the association between dietary fiber intake and risk of breast cancer (BC) by menopausal status and hormone receptor expression in tumors.

Objective: We investigated the relation between total dietary fiber and its main food sources (vegetables, fruit, cereals, and legumes) and BC risk by using data from the European Prospective Investigation into Cancer and Nutrition (EPIC).

Design: A total of 11,576 invasive BC cases in 334,849 EPIC women mostly aged 35–70 y at baseline were identified over a median follow-up of 11.5 y. Dietary fiber was estimated from country-specific dietary questionnaires. Multivariable Cox proportional hazards regression models were used to quantify the association between dietary variables and BC risk with energy adjustment by using the residual method. Subgroup analyses were performed by menopausal status and estrogen receptor (ER) and progesterone receptor (PR) expression in tumors.

Results: BC risk was inversely associated with intakes of total dietary fiber [hazard ratio comparing fifth quintile to first quintile ($HR_{Q5\text{-}Q1}$): 0.95; 95% CI: 0.89, 1.01; *P*-trend = 0.03] and fiber from vegetables (0.90; 0.84, 0.96; *P*-trend < 0.01) but not with fiber from fruit, cereals, or legumes. Overall, associations were homogeneous by menopausal status and ER and PR expression in tumors. For vegetable fiber, stronger associations were observed for estrogen receptor–negative and progesterone receptor–negative ($HR_{Q5\text{-}Q1}$:0.74; 95% CI: 0.59, 0.93; *P*-trend = 0.01) than for estrogen receptor–positive and progesterone receptor–positive tumors (0.92: 0.81, 1.03; *P*-trend = 0.05), with *P*-heterogeneity = 0.09.

Conclusion: Diets rich in dietary fiber and, particularly, fiber from vegetables may be associated with a small reduction in risk of BC, independently of menopausal status. *Am J Clin Nutr* 2013;97:344–53.

Am J Clin Nutr 2013;97:344–53.

Dietary Fat Intake and Development of Specific Breast Cancer Subtypes

Sabina Sieri, Paolo Chiodini, Claudia Agnoli, Valeria Pala, Franco Berrino, Antonia Trichopoulou, Vassiliki Benetou, Effie Vasilopoulou, María-José Sánchez, Maria-Dolores Chirlaque, Pilar Amiano, J. Ramón Quirós, Eva Ardanaz, Genevieve Buckland, Giovanna Masala, Salvatore Panico, Sara Grioni, Carlotta Sacerdote, Rosario Tumino, Marie-Christine Boutron-Ruault, Françoise Clavel-Chapelon, Guy Fagherazzi, Petra H. M. Peeters, Carla H. van Gils, H. Bas Bueno-de-Mesquita, Henk J. van Kranen, Timothy J. Key, Ruth C. Travis, KayTee Khaw, Nicholas J. Wareham, Rudolf Kaaks, Annekatrin Lukanova, Heiner Boeing, Madlen Schütze, Emily Sonestedt, Elisabeth Wirfält, Malin Sund, Anne Andersson, Veronique Chajes, Sabina Rinaldi, Isabelle Romieu, Elisabete Weiderpass, Guri Skeie, Engeset Dagrun, Anne Tjønneland, Jytte Halkjær, Kim Overvard, Melissa A. Merritt, David Cox, Elio Riboli, Vittorio Krogh

We prospectively evaluated fat intake as predictor of developing breast cancer (BC) subtypes defined by estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 receptor (HER2), in a large (n = 337 327) heterogeneous cohort of women, with 10 062 BC case patients after 11.5 years, estimating BC hazard ratios (HRs) by Cox proportional hazard modeling. High total and saturated fat were associated with greater risk of ER^+PR^+ disease (HR = 1.20, 95% confidence interval [CI] = 1.00 to 1.45; HR = 1.28, 95% CI = 1.09 to 1.52; highest vs lowest quintiles) but not ER^-PR^- disease. High saturated fat was statistically significantly associated with greater risk of $HER2^-$ disease. High saturated fat intake particularly increases risk of receptor-positive disease, suggesting saturated fat involvement in the etiology of this BC subtype.

JNCI J Natl Cancer Inst (2014) 106(5): dju068 doi:10.1093/jnci/dju068

L'iperinsulinemia e l'insulinoresistenza sono state implicate nella patogenesi di numerose patologie croniche.

Tipi diversi di carboidrati possono determinare una diversa risposta glicemica

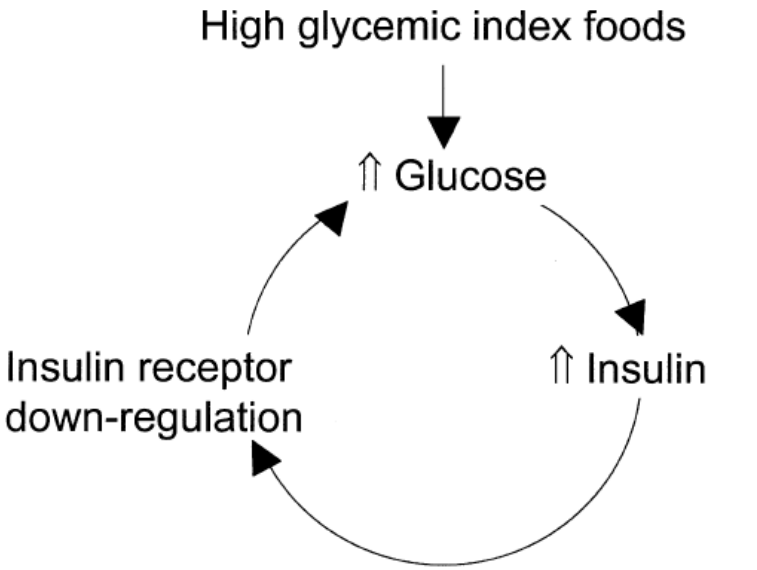


Figure 1 Potential mechanism for the relationship between high glycemic index foods and insulin resistance. (Adapted from Jenkins *et al*, 2000).

Augustin et al, European J Clin Nutr 2002

Table 2 Glycemic indices of some common foods

Food	GI_{wb}	GI_g
Sucrose	92	67
Glucose	138	100
Fructose	32	23
Honey	104	75
Milk	39	28
Beans	40–60	30–43
Lentils	30–40	22–30
Pasta	50–70	36–51
Pizza	86	62
Cornmeal/cornflakes	100–120	72–87
White bread	100	72
Pumpernickel	58	42
Potatoes	120	87
Banana, ripe	85	62
Banana, underripe	43	31
Oranges	62	45
Grapefruit	36	26
Cherries	32	23
Tomatoes	13	9

GI_{wb}, standard food: white bread. GI_g, standard food: glucose ($GI_g = GI_{wb}/1.38$).

Indice Glicemico e Carico Glicemico della dieta sono aspetti attualmente particolarmente studiati in relazione al rischio di diverse patologie croniche inclusi i tumori

Nella componente italiana dello studio EPIC è stata valutata l'**associazione tra Indice Glicemico e Carico Glicemico della dieta e rischio di tumore della mammella** (follow up di circa 11 anni ; 879 tumori)

- un **elevato Carico Glicemico** della dieta è risultato associato ad un aumento di rischio (HR 1.45, 95% IC1.06-1.99; p-trend 0.029),
- l'associazione non era modificata dal valore dell'Indice di Massa Corporea né dallo stato menopausale.

Questi dati suggeriscono che in una popolazione mediterranea tradizionalmente caratterizzata da un elevato consumo di carboidrati complessi, questi indici possono fornire indicazioni sul livello del rischio specifico

Sieri S *et al.* "High Glycemic diet and breast cancer occurrence in the Italian EPIC cohort"
***Nutr Metab Cardiovasc Dis*, 2012**

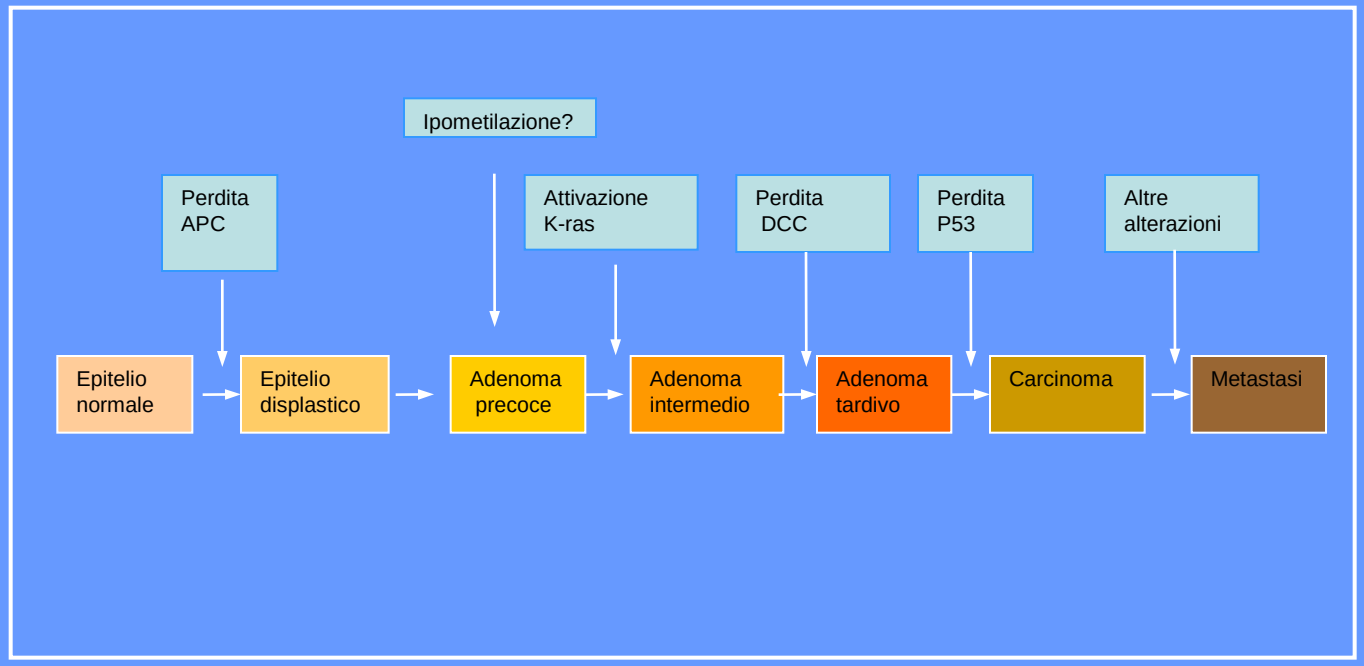
IL TUMORE DEL

COLON RETTO

- Il CCR ha una storia naturale di lunga durata nel corso della quale è a lungo asintomatico ma potenzialmente diagnosticabile e guaribile.

- La prevenzione riveste quindi un'importanza strategica nella lotta a questo tumore e nella programmazione sanitaria.

IL MODELLO DI VOGELSTEIN



La probabilità di trasformazione ammonta a circa il 15% per gli adenomi con diametro superiore ad 1cm.

FATTORI DI RISCHIO PER IL TUMORE DEL COLONRETTO

- ✓ Età
- ✓ Familiarità
- ✓ **Alimenti e gruppi di alimenti:** carni rosse, bevande alcoliche
- ✓ **Nutrienti:** grassi saturi, alcol
- ✓ Fumo di sigaretta
- ✓ Sedentarietà
- ✓ **Antropometria:** BMI, circonferenza vita, ecc.
- ✓ Altro: diabete mellito, ecc.
- ✓ IBD / MICI (Retto-Colite Ulcerosa, Morbo di Crohn) ??

FATTORI PROTETTIVI PER IL TUMORE DEL COLONRETTO

- ✓ **Alimenti e gruppi di alimenti:** verdura e frutta fresca, legumi, pesce, latticini
- ✓ **Nutrienti:** (fibre alimentari), calcio e vitamina D, vitamine B6, C, E, acido folico
- ✓ **Stile di Vita**: Attività fisica
- ✓ Altri fattori: "gut microbiota", assunzione di FANS, HRT, contraccettivi orali.

World Cancer Research Fund

CUP Continuous Update Project

Analysing research on cancer prevention and survival

FOOD, NUTRITION, PHYSICAL ACTIVITY AND CANCERS OF THE COLON AND THE RECTUM 2011

	DECREASES RISK	INCREASES RISK
Convincing	**Physical activity[1,2]** **Foods containing dietary fibre[3]**	**Red meat[4,5]** **Processed meat[4,6]** **Alcoholic drinks (men)[7]** **Body fatness** **Abdominal fatness** **Adult attained height[8]**
Probable	Garlic Milk[9] Calcium[10]	**Alcoholic drinks (women)[7]**
Substantial effect on risk unlikely	None identified	

1 Physical activity of all types: occupational, household, transport and recreational.

2 The Panel judges that the evidence for colon cancer is convincing. No conclusion was drawn for rectal cancer.

3 Includes both foods naturally containing the constituent and foods which have the constituent added. Dietary fibre is contained in plant foods.

4 Although red and processed meats contain iron, the general category of 'foods containing iron' comprises many other foods, including those of plant origin.

5 The term 'red meat' refers to beef, pork, lamb, and goat from domesticated animals.

6 The term 'processed meat' refers to meats preserved by smoking, curing, or salting, or addition of chemical preservatives.

7 The judgements for men and women are different because there are fewer data for women. For colorectal and colon cancers the effect appears stronger in men than in women.

8 Adult attained height is unlikely directly to modify the risk of cancer. It is a marker for genetic, environmental, hormonal, and also nutritional factors affecting growth during the period from preconception to completion of linear growth (see chapter 6.2.13 – Second Expert Report).

9 Milk from cows. Most data are from high-income populations, where calcium can be taken to be a marker for milk/dairy consumption. The Panel judges that a higher intake of dietary calcium is one way in which milk could have a protective effect.

10 The evidence is derived from studies using supplements at a dose of 1200mg/day.

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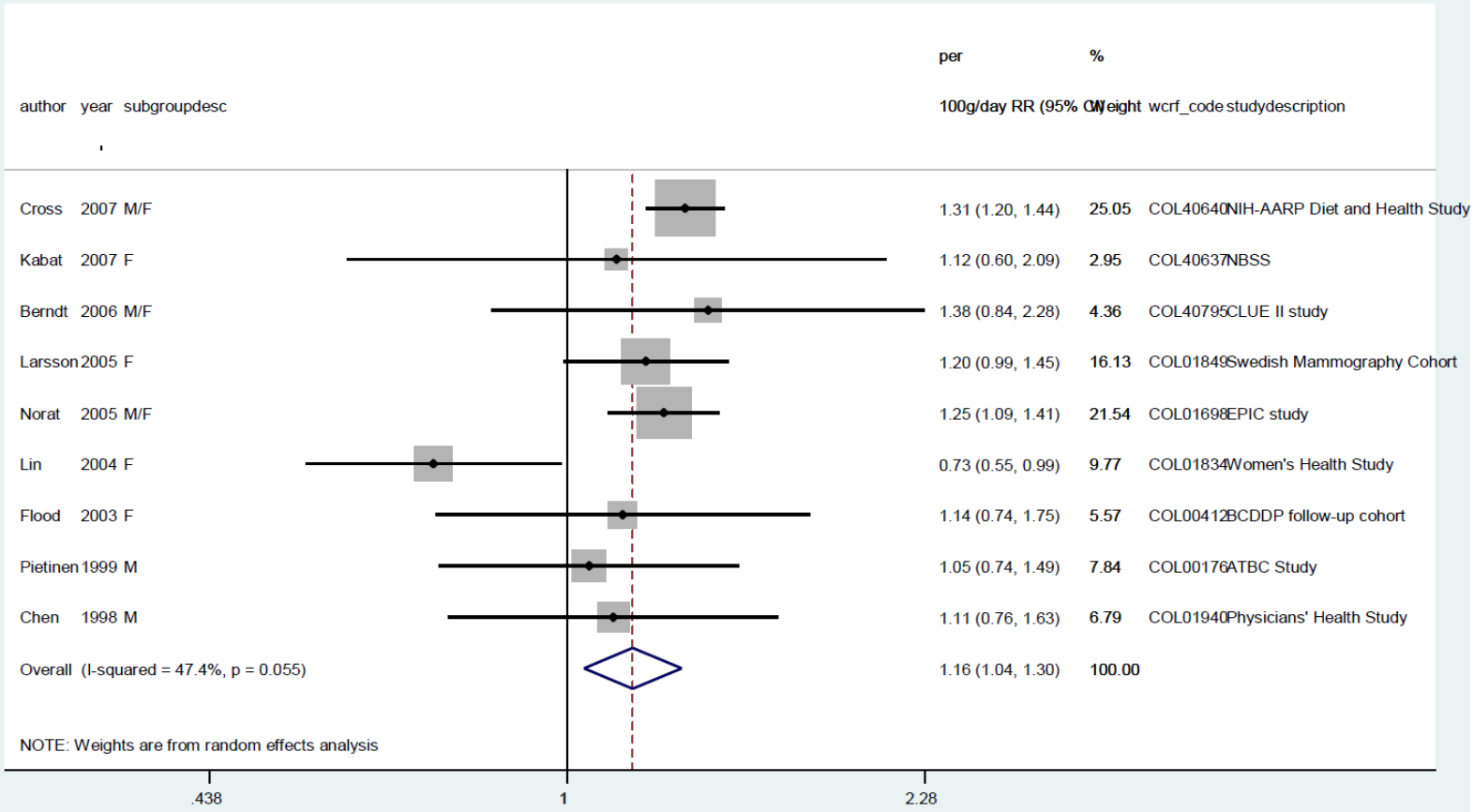
CARNI ROSSE E CONSERVATE

La metanalisi del Continous Update Project (CUP) relativa al consumo di **carni rosse e conservate** ha mostrato nel CCR un incremento del rischio del 16% (per incrementi di 100g/d).

Figure 47 Dose-response meta-analysis of red and processed meat and colorectal cancer – per 100g/d



Journal of the National Cancer Institute, Vol. 97, No. 12, June 15, 2005

Meat, Fish, and Colorectal Cancer Risk: The European Prospective Investigation into Cancer and Nutrition

Teresa Norat, Sheila Bingham, Pietro Ferrari, Nadia Slimani, Mazda Jenab, Mathieu Mazuir, Kim Overvad, Anja Olsen, Anne Tjønneland, Francoise Clavel, Marie-Christine Boutron-Ruault, Emmanuelle Kesse, Heiner Boeing, Manuela M. Bergmann, Alexandra Nieters, Jakob Linseisen, Antonia Trichopoulou, Dimitrios Trichopoulos, Yannis Tountas, Franco Berrino, Domenico Palli, Salvatore Panico, Rosario Tumino, Paolo Vineis, H. Bas Bueno-de-Mesquita, Petra H. M. Peeters, Dagrun Engeset, Eiliv Lund, Guri Skeie, Eva Ardanaz, Carlos González, Carmen Navarro, J. Ramón Quirós, María-José Sanchez, Göran Berglund, Irene Mattisson, Göran Hallmans, Richard Palmqvist, Nicholas E. Day, Kay-Tee Khaw, Timothy J. Key, Miguel San Joaquin, Bertrand Hémon, Rodolfo Saracci, Rudolf Kaaks, Elio Riboli

Background: **Current evidence suggests that high red meat intake is associated with increased colorectal cancer risk. High fish intake may be associated with a decreased risk, but the existing evidence is less convincing.** *Methods:* **We prospectively followed 478 040 men and women from 10 European countries who were free of cancer at enrollment between 1992 and 1998. Information on diet and lifestyle was collected at baseline. After a mean follow-up of 4.8 years, 1329 incident colorectal cancers were documented. We examined the relationship between intakes of red and processed meat, poultry, and fish and colorectal cancer risk using a proportional hazards model adjusted for age, sex, energy (nonfat and fat sources), height, weight, work-related physical activity, smoking status, dietary fiber and folate, and alcohol consumption, stratified by center. A calibration substudy based on 36 994 subjects was used to correct hazard ratios (HRs) and 95% confidence intervals (CIs) for diet measurement errors. All statistical tests were two-sided.** *Results:* **Colorectal cancer risk was positively associated with intake of red and processed meat (highest [>160 g/day] versus lowest [<20 g/day] intake, HR = 1.35, 95% CI = 0.96 to 1.88; P_{trend} = .03) and inversely associated with intake of fish (>80 g/day versus <10 g/day, HR = 0.69, 95 % CI = 0.54 to 0.88; P_{trend}<.001), but was not related to poultry intake. Correcting for measurement error strengthened the associations between colorectal cancer and red and processed meat intake (per 100-g increase HR = 1.25, 95% CI =1.09 to 1.41, P_{trend} = .001 and HR = 1.55, 95% CI = 1.19 to 2.02, P_{trend} = .001 before and after calibration, respectively) and for fish (per 100 g increase HR = 0.70, 95% CI = 0.57 to 0.87, P_{trend}<.001 and HR = 0.46, 95% CI = 0.27 to 0.77, P_{trend} = .003; before and after correction, respectively). In this study population, the absolute risk of development of colorectal cancer within 10 years for a study subject aged 50 years was 1.71% for the highest category of red and processed meat intake and 1.28% for the lowest category of intake and was 1.86% for subjects in the lowest category of fish intake and 1.28% for subjects in the highest category of fish intake.** *Conclusions:* **Our data confirm that colorectal cancer risk is positively associated with high consumption of red and processed meat and support an inverse association with fish intake.**

[J Natl Cancer Inst 2005;97:906–16]

Table 4. Multivariable hazard ratios (HRs, per 100 g) and 95% confidence intervals (CIs) of colorectal cancer for observed and calibrated intakes of red meat, processed meat, fish, and poultry by anatomic location for participants in the European Prospective Investigation into Cancer and Nutrition (EPIC)*

		Observed		Calibrated	
Food group	Cancer site	HR (95% CI), per 100 g	P_{trend}	HR (95% CI), per 100 g	P_{trend}
Red and processed meat	Colorectum	1.25 (1.09 to 1.41)	.001	1.55 (1.19 to 2.02)	.001
	Colon	1.26 (1.07 to 1.48)	.006	1.49 (1.03 to 2.16)	.04
	Rectum	1.22 (0.99 to 1.51)	.06	1.65 (1.05 to 2.62)	.03
Red meat	Colorectum	1.21 (1.02 to 1.43)	.03	1.49 (0.91 to 2.43)	.11
	Colon	1.20 (0.96 to 1.48)	.10	1.36 (0.74 to 2.50)	.32
	Rectum	1.23 (0.94 to 1.62)	.14	1.75 (0.93 to 3.30)	.08
Processed meat	Colorectum	1.32 (1.07 to 1.63)	.009	1.70 (1.05 to 2.76)	.03
	Colon	1.39 (1.06 to 1.82)	.01	1.68 (0.87 to 3.27)	.12
	Rectum	1.22 (0.87 to 1.71)	.25	1.70 (0.83 to 3.47)	.14
Fish	Colorectum	0.70 (0.57 to 0.87)	<.001	0.46 (0.27 to 0.77)	.003
	Colon	0.76 (0.59 to 0.99)	.04	0.49 (0.26 to 0.93)	.03
	Rectum	0.61 (0.43 to 0.87)	.006	0.41 (0.17 to 0.97)	.04
Poultry	Colorectum	0.92 (0.68 to 1.25)	.61	0.85 (0.43 to 1.70)	.65
	Colon	0.92 (0.63 to 1.35)	.68	0.76 (0.29 to 2.03)	.59
	Rectum	0.92 (0.56 to 1.53)	.77	1.04 (0.34 to 3.23)	.94

*Cox regression with age as primary time variable. Covariates are sex, energy from fat, energy from -nonfat sources except alcohol, height (tertiles defined by sex and center), weight (tertiles defined by sex and center), current alcohol intake (g/day), occupational physical activity, smoking status (never, former, or current smoker), and fiber intake. Stratification by center.

da Norat et al, 2005

Meccanismi ipotizzati per l'associazione fra CCR e carni rosse

- Maggior potenziale di nitrosazione del **ferro emico** rispetto al ferro inorganico (> nitrosazione endogena). L'eme è in grado anche di danneggiare la mucosa colica e stimolare la proliferazione cellulare

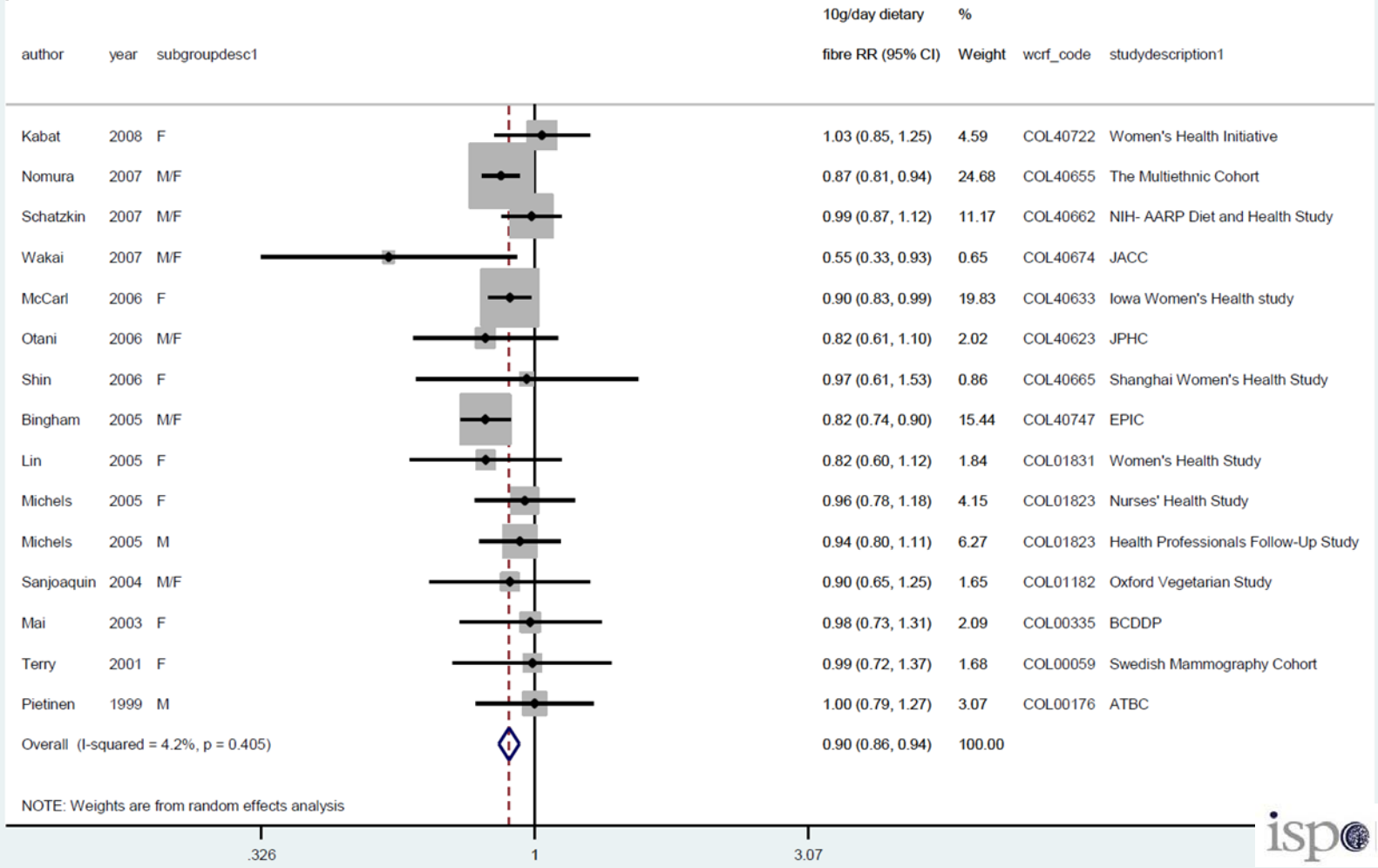
- Possibile **effetto cancerogeno di amine eterocicliche e idrocarburi policiclici aromatici** (formati come prodotto secondario durante i processi di cottura ad alte temperature, in particolare mediante grill o barbecue)

- Alle carni processate vengono aggiunte molte **sostanze a fini di conservazione**, fra le quali nitrati e nitriti, con conseguente aumento dei livelli fecali di N-nitroso composti

FIBRE

La metanalisi CUP relativa al **consumo di fibre** ha mostrato una riduzione del 10% del rischio nel CCR (per incrementi di 10g/d)

Figure 125 Dose-response meta-analysis of dietary fibre and colorectal cancer – per 10g/day



ISTITUTO PER LO STUDIO E LA PREVENZIONE ONCOLOGICA

Dietary fibre in food and protection against colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC): an observational study

Sheila A Bingham, Nicholas E Day, Robert Luben, Pietro Ferrari, Nadia Slimani, Teresa Norat, Françoise Clavel-Chapelon, Emmanuelle Kesse, Alexandra Nieters, Heiner Boeing, Anne Tjønneland, Kim Overvad, Carmen Martinez, Miren Dorronsoro, Carlos A Gonzalez, Timothy J Key, Antonia Trichopoulou, Androniki Naska, Paolo Vineis, Rosario Tumino, Vittorio Krogh, H Bas Bueno-de-Mesquita, Petra HM Peeters, Göran Berglund, Göran Hallmans, Eiliv Lund, Guri Skeie, Rudolf Kaaks, Elio Riboli

Summary

Background Dietary fibre is thought to protect against colorectal cancer but this view has been challenged by recent prospective and intervention studies that showed no protective effect.

Methods We prospectively examined the association between dietary fibre intake and incidence of colorectal cancer in 519 978 individuals aged 25–70 years taking part in the EPIC study, recruited from ten European countries. Participants completed a dietary questionnaire in 1992–98 and were followed up for cancer incidence. Relative risk estimates were obtained from fibre intake, categorised by sex-specific, cohort-wide quintiles, and from linear models relating the hazard ratio to fibre intake expressed as a continuous variable.

Findings Follow-up consisted of 1 939 011 person-years, and data for 1065 reported cases of colorectal cancer were included in the analysis. Dietary fibre in foods was inversely related to incidence of large bowel cancer (adjusted relative risk 0·75 [95% CI 0·59–0·95] for the highest versus lowest quintile of intake), the protective effect being greatest for the left side of the colon, and least for the rectum. After calibration with more detailed dietary data, the adjusted relative risk for the highest versus lowest quintile of fibre from food intake was 0·58 (0·41–0·85). No food source of fibre was significantly more protective than others, and non-food supplement sources of fibre were not investigated.

Interpretation In populations with low average intake of dietary fibre, an approximate doubling of total fibre intake from foods could reduce the risk of colorectal cancer by 40%.

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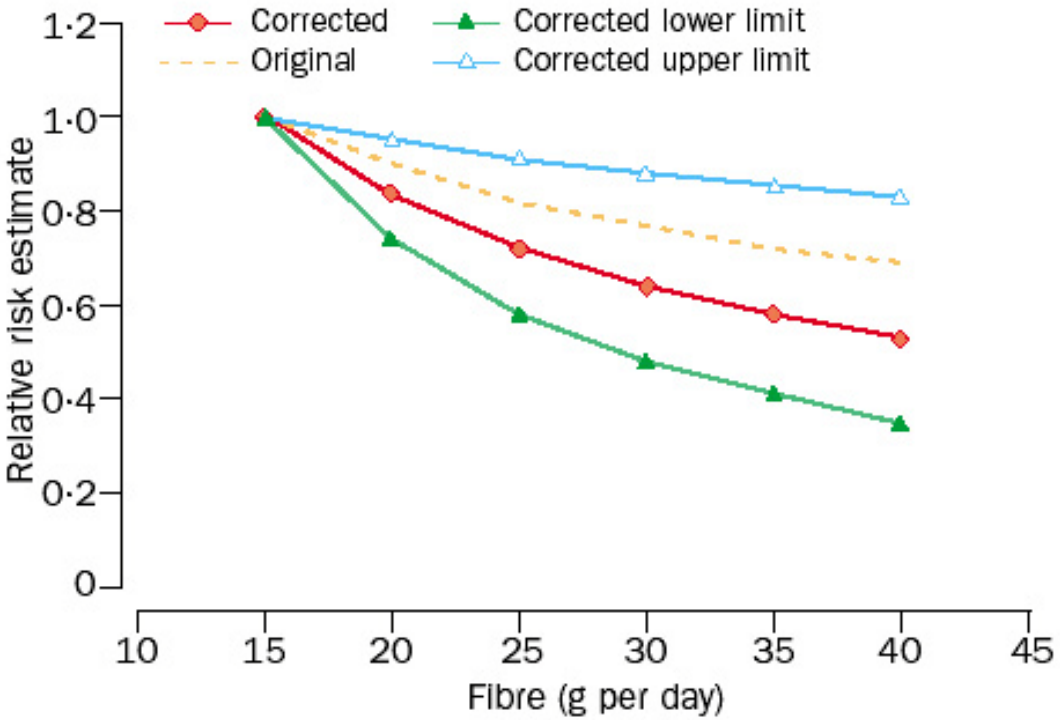

Figure 1: **Relative risk for colorectal cancer according to dietary fibre intake**

Calculated from Cox's regression using age, weight, height, sex, non-fat energy, energy from fat. Original estimates are calculated from the hazard ratio[20] for each quintile increase in energy adjusted fibre (table 3).

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Meccanismi ipotizzati per l'associazione fra CCR e assunzione di fibra

- La fibra alimentare aumenta il **volume delle feci**, riduce il tempo di transito, diluisce il contenuto colico, tutti effetti che determinano un minor contatto fra i composti presenti nel materiale fecale e la mucosa colica.

- Stimola la fermentazione batterica (> "**gut microbiota**") con maggior produzione di acidi grassi a catena corta (es *butirrato*), riduzione del pH e minor conversione degli acidi biliari primari in acidi biliari secondari.

- Il *butirrato* possiede proprietà pro-apoptotiche e anti-proliferative.

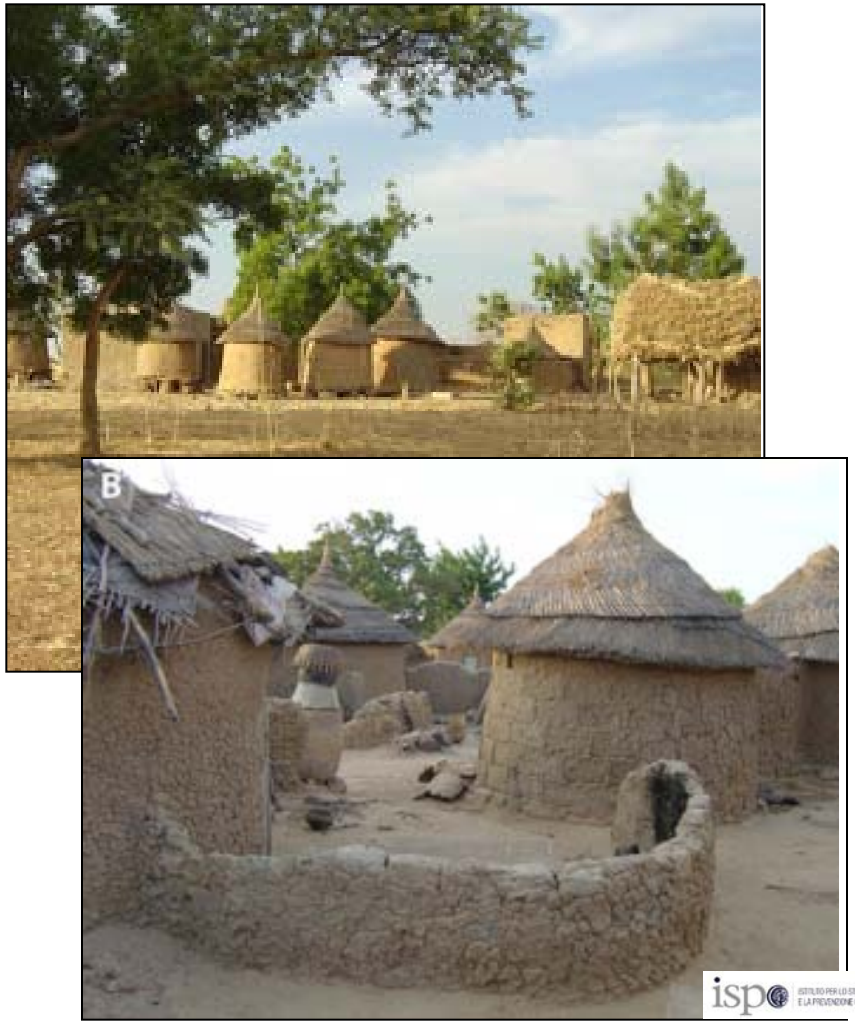
- Alimenti ricchi in fibra hanno (in genere) **basso indice glicemico** riducono **il carico glicemico** della dieta e quindi i livelli di insulina

Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa

PNAS | August 17, 2010 | vol. 107 | no. 33 | 14691–14696

Carlotta De Filippo[a], Duccio Cavalieri[a], Monica Di Paola[b], Matteo Ramazzotti[c], Jean Baptiste Poullet[d], Sebastien Massart[d], Silvia Collini[b], Giuseppe Pieraccini[e], and Paolo Lionetti[b,1]

Gut microbial composition depends on different dietary habits just as health depends on microbial metabolism, but the association of microbiota with different diets in human populations has not yet been shown. In this work, we compared the fecal microbiota of European children (EU) and that of children from a rural African village of Burkina Faso (BF), where the diet, high in fiber content, is similar to that of early human settlements at the time of the birth of agriculture. By using high-throughput 16S rDNA sequencing and biochemical analyses, we found significant differences in gut microbiota between the two groups. BF children showed a significant enrichment in Bacteroidetes and depletion in Firmicutes ($P < 0.001$), with a unique abundance of bacteria from the genus *Prevotella* and *Xylanibacter*, known to contain a set of bacterial genes for cellulose and xylan hydrolysis, completely lacking in the EU children. In addition, we found significantly more short-chain fatty acids ($P < 0.001$) in BF than in EU children. Also, *Enterobacteriaceae* (*Shigella* and *Escherichia*) were significantly underrepresented in BF than in EU children ($P < 0.05$). We hypothesize that gut microbiota coevolved with the polysaccharide-rich diet of BF individuals, allowing them to maximize energy intake from fibers while also protecting them from inflammations and noninfectious colonic diseases. This study investigates and compares human intestinal microbiota from children characterized by a modern western diet and a rural diet, indicating the importance of preserving this treasure of microbial diversity from ancient rural communities worldwide.



Dietary glycemic index and glycemic load and risk of colorectal cancer: results from the EPIC-Italy study.

Sieri S, Krogh V, Agnoli C, Ricceri F, Palli D, Masala G, Panico S, Mattiello A, Tumino R, Giurdanella MC, Brighenti F, Scazzina F, Vineis P, Sacerdote C.

Int J Cancer. 2015;136:2923-31

A carbohydrate-rich diet, resulting in high blood glucose and insulin, has been hypothesized as involved in colorectal cancer etiology. We investigated dietary glycemic index (GI) and glycemic load (GL), in relation to colorectal cancer, in the prospectively recruited EPIC-Italy cohort. **After a median 11.7 years, 421 colorectal cancers were diagnosed among 47,749 recruited adults**. GI and GL were estimated from validated food frequency questionnaires. Multivariable Cox modeling estimated hazard ratios (HRs) for associations between colorectal cancer and intakes of total, high GI and low GI carbohydrate and GI and GL. The adjusted HR of colorectal cancer for highest versus lowest GI quartile was 1.35; 95% confidence interval (CI) 1.03-1.78; p trend 0.031. Increasing high GI carbohydrate intake was also significantly associated with increasing colorectal cancer risk (HR 1.45; 95% CI 1.04-2.03; p trend 0.034), whereas increasing low GI carbohydrate was associated with reducing risk (HR 0.73; 95% CI 0.54-0.98; p trend 0.033). High dietary GI and high GI carbohydrate were associated with increased risks of cancer at all colon sites (HR 1.37; 95% CI 1.00-1.88, HR 1.80; 95% CI 1.22-2.65, respectively), whereas high GI carbohydrate and high GL were associated with increased risk of proximal colon cancer (HR 1.94; 95% CI 1.18-3.16, HR 2.01; 95% CI 1.08-3.74, respectively). After stratification for waist-to-hip ratio (WHR), cancer was significantly associated with GI, and high GI carbohydrate, in those with high WHR. These findings suggest that **high dietary GI and high carbohydrate intake from high GI foods are associated with increased risk of colorectal cancer.**

FRUTTA E VERDURA

Numerosi studi sia caso-controllo che di coorte hanno indagato l'associazione tra consumi elevati di frutta e/o verdura e rischio di CCR con risultati contrastanti.

Una associazione inversa con elevati consumi è stata suggerita per

- ***crucifere***
- ***verdure verdi***
- ***aglio***
- ***agrumi***

Frutta e verdura sono ricchi di composti per i quali è ipotizzabile un effetto anti-cancerogeno: **fibre, folati, indolo, carotenoidi, vitamina C, flavonoidi, fitoestrogeni.**

E' difficile valutare separatamente l'importanza relativa dei vari costituenti ed è possibile che l'effetto protettivo derivi dalla combinazione dell'effetto di più composti.

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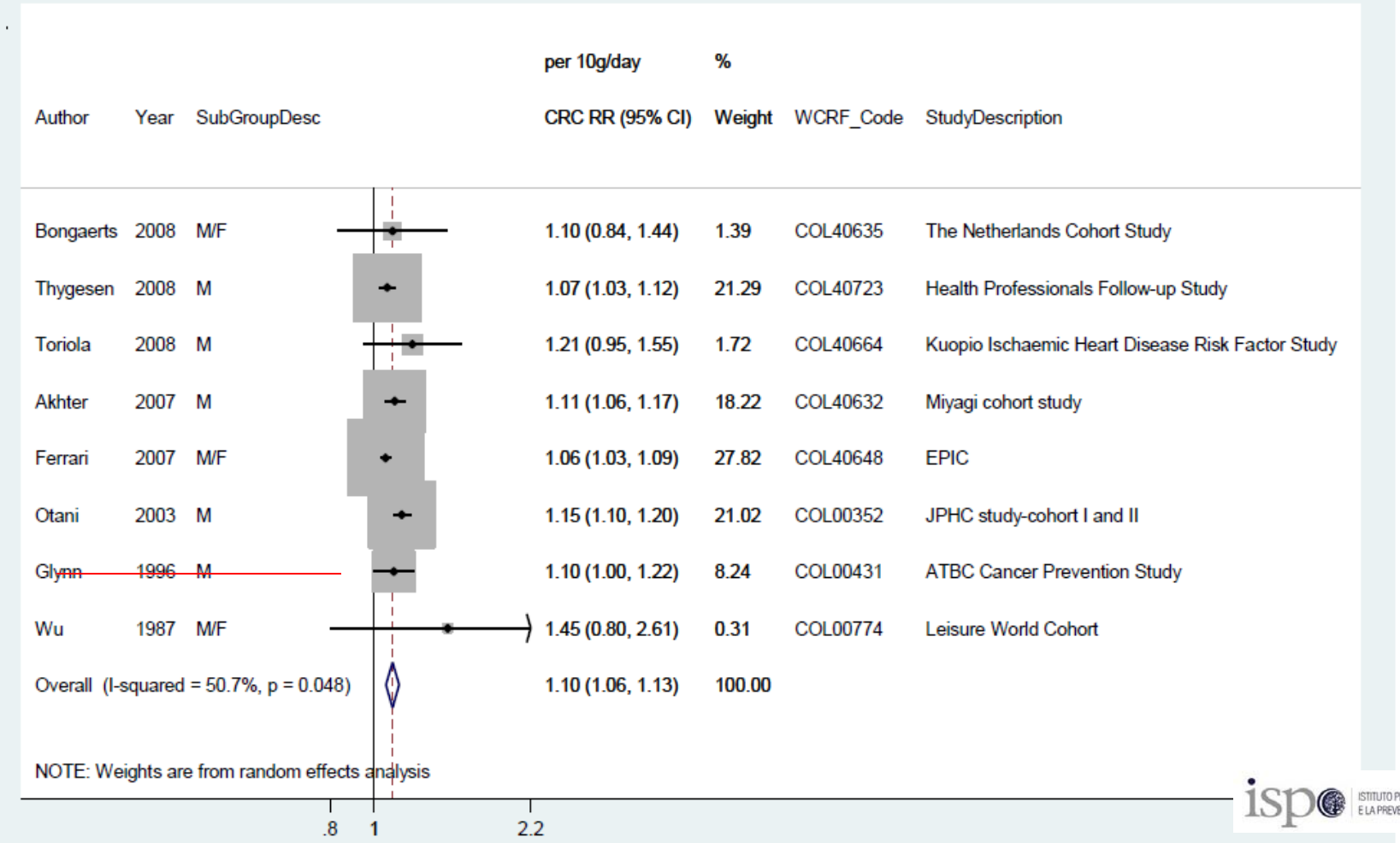
ALCOL

La metanalisi CUP relativa al **consumo di alcol** evidenzia nel CCR un significativo aumento del rischio del 10% (per incrementi di 10g/d)

Figure 208 Dose-response meta-analysis of alcohol (as ethanol) and colorectal cancer - per 10g/day



Int. J. Cancer: **121,** 2065–2072 (2007)

Lifetime and baseline alcohol intake and risk of colon and rectal cancers in the European Prospective Investigation into Cancer and Nutrition (EPIC)

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Alcohol consumption may be associated with risk of colorectal cancer (CRC), but the epidemiological evidence for an association with specific anatomical subsites, types of alcoholic beverages and current *vs.* lifetime alcohol intake is inconsistent. Within the European Prospective Investigation into Cancer and Nutrition (EPIC), 478,732 study subjects free of cancer at enrolment between 1992 and 2000 were followed up for an average of 6.2 years, during which 1,833 CRC cases were observed. Detailed information on consumption of alcoholic beverages at baseline (all cases) and during lifetime (1,447 CRC cases, 69% of the cohort) was collected from questionnaires. Cox proportional hazard models were used to examine the alcohol-CRC association. After adjustment for potential confounding factors, lifetime alcohol intake was significantly positively associated to CRC risk (hazard ratio, HR = 1.08, 95%CI = 1.04–1.12 for 15 g/day increase), with higher cancer risks observed in the rectum (HR = 1.12, 95%CI = 1.06–1.18) than distal colon (HR = 1.08, 95%CI = 1.01–1.16), and proximal colon (HR = 1.02, 95%CI = 0.92–1.12). Similar results were observed for baseline alcohol intake. When assessed by alcoholic beverages at baseline, the CRC risk for beer (HR = 1.38, 95%CI = 1.08–1.77 for 20–39.9 *vs.* 0.1–2.9 g/day) was higher than wine (HR = 1.21, 95%CI = 1.02–1.44), although the two risk estimates were not significantly different from each other. Higher HRs for baseline alcohol were observed for low levels of folate intake (1.13, 95%CI = 1.06–1.20 for 15 g/day increase) compared to high folate intake (1.03, 95%CI = 0.98–1.09). In this large European cohort, both lifetime and baseline alcohol consumption increase colon and rectum cancer risk, with more apparent risk increases for alcohol intakes greater than 30 g/day.

ANTROPOMETRIA

- Numerosi studi hanno evidenziato un aumento di rischio per CCR in relazione **all'aumento di peso o indice di massa corporea (BMI)**

- Il rischio appare più elevato per il **colon**

- Diverse misure di **obesità** centrale e periferica sono state associate ad un aumento di rischio per lo sviluppo di CRC, anche in tal caso con importanti distinzioni per sesso e sede anatomica.

- Nello studio EPIC le diverse misure di adiposità centrale e periferica si associano ad un aumento di cancro del colon nei maschi di circa il 50%.
  Pischon T, Riboli E, et al., J Natl Cancer Inst 2006 Jul 5;98(13):920-31

Journal of the National Cancer Institute, Vol. 98, No. 13, July 5, 2006

Body Size and Risk of Colon and Rectal Cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC)

Tobias Pischon, Petra H. Lahmann, Heiner Boeing, Christine Friedenreich, Teresa Norat, Anne Tjønneland, Jytte Halkjaer, Kim Overvad, Françoise Clavel-Chapelon, Marie-Christine Boutron-Ruault, Gregory Guernec, Manuela M. Bergmann, Jakob Linseisen, Nikolaus Becker, Antonia Trichopoulou, Dimitrios Trichopoulos, Sabina Sieri, Domenico Palli, Rosario Tumino, Paolo Vineis, Salvatore Panico, Petra H. M. Peeters, H. Bas Bueno-de-Mesquita, Hendriek C. Boshuizen, Bethany Van Guelpen, Richard Palmqvist, Göran Berglund, Carlos Alberto Gonzalez, Miren Dorronsoro, Aurelio Barricarte, Carmen Navarro, Carmen Martinez, J. Ramón Quirós, Andrew Roddam, Naomi Allen, Sheila Bingham, Kay-Tee Khaw, Pietro Ferrari, Rudolf Kaaks, Nadia Slimani, Elio Riboli

Background: **Body weight and body mass index (BMI) are positively related to risk of colon cancer in men, whereas weak or no associations exist in women. This discrepancy may be related to differences in fat distribution between sexes or to the use of hormone replacement therapy (HRT) in women.** ***Methods:*** **We used multivariable adjusted Cox proportional hazards models to examine the association between anthropometric measures and risks of colon and rectal cancer among 368 277 men and women who were free of cancer at baseline from nine countries of the European Prospective Investigation Into Cancer and Nutrition. All statistical tests were two-sided.** ***Results:*** **During 6.1 years of follow-up, we identified 984 and 586 patients with colon and rectal cancer, respectively. Body weight and BMI were statistically significantly associated with colon cancer risk in men (highest versus lowest quintile of BMI, relative risk [RR] = 1.55, 95% confidence interval [CI] = 1.12 to 2.15; P_{trend} = .006) but not in women. In contrast, comparisons of the highest to the lowest quintile showed that several anthropometric measures, including waist circumference (men, RR = 1.39, 95% CI = 1.01 to 1.93; P_{trend} = .001; women, RR = 1.48, 95% CI = 1.08 to 2.03; P_{trend} = .008), waist-to-hip ratio (WHR; men, RR = 1.51, 95% CI = 1.06 to 2.15; P_{trend} = .006; women, RR = 1.52, 95% CI = 1.12 to 2.05; P_{trend} = .002), and height (men, RR = 1.40, 95% CI = 0.99 to 1.98; P_{trend} = .04; women, RR = 1.79, 95% CI = 1.30 to 2.46; P_{trend}<.001) were related to colon cancer risk in both sexes. The estimated absolute risk of developing colon cancer within 5 years was 203 and 131 cases per 100 000 men and 129 and 86 cases per 100 000 women in the highest and lowest quintiles of WHR, respectively. Upon further stratification, no association of waist circumference and WHR with risk of colon cancer was observed among postmenopausal women who used HRT. None of the anthropometric measures was statistically significantly related to rectal cancer.** ***Conclusions:*** **Waist circumference and WHR, indicators of abdominal obesity, were strongly associated with colon cancer risk in men and women in this population. The association of abdominal obesity with colon cancer risk may vary depending on HRT use in postmenopausal women; however, these findings require confirmation in future studies. [J Natl Cancer Inst 2006;98:920–31]**

Indici antropometrici e rischio di CCR
EPIC Europa (Pischon et al, 2006)

Journal of the National Cancer Institute, Vol. 98, No. 13, July 5, 2006

Men				Women			
Measure	N*	Crude RR (95% CI)†	Multivariable RR (95% CI)‡	Measure	N*	Crude RR (95% CI)†	Multivariable RR (95% CI)‡
Height, cm				Height, cm			
<168.0	79	1 (Referent)	1 (Referent)	<156.0	80	1 (Referent)	1 (Referent)
168.0–172.4	84	1.09 (0.79 to 1.50)	1.10 (0.80 to 1.52)	156.0–159.9	106	1.34 (0.99 to 1.80)	1.33 (0.99 to 1.80)
172.5–176.1	86	1.14 (0.82 to 1.57)	1.16 (0.84 to 1.60)	160.0–163.2	141	1.72 (1.29 to 2.30)	1.71 (1.28 to 2.28)
176.2–180.4	91	1.26 (0.91 to 1.74)	1.29 (0.93 to 1.79)	163.3–167.4	128	1.68 (1.25 to 2.27)	1.66 (1.23 to 2.24)
≥180.5	81	1.33 (0.95 to 1.87)	1.40 (0.99 to 1.98)	≥167.5	108	1.82 (1.33 to 2.50)	1.79 (1.30 to 2.46)
P_{trend}§		.06	.04	P_{trend}§		<.001	<.001
Weight, kg				Weight, kg			
<71.0	72	1 (Referent)	1 (Referent)	<56.9	83	1 (Referent)	1 (Referent)
71.0–76.9	68	0.94 (0.67 to 1.31)	0.91 (0.65 to 1.28)	56.9–62.0	100	1.20 (0.89 to 1.60)	1.14 (0.84 to 1.53)
77.0–82.7	79	1.12 (0.81 to 1.54)	1.06 (0.76 to 1.48)	62.1–67.4	108	1.19 (0.89 to 1.59)	1.10 (0.82 to 1.49)
82.8–89.9	93	1.33 (0.97 to 1.82)	1.24 (0.89 to 1.73)	67.5–74.9	137	1.35 (1.02 to 1.78)	1.23 (0.91 to 1.64)
≥90.0	109	1.57 (1.16 to 2.13)	1.43 (1.02 to 2.02)	≥75.0	135	1.40 (1.06 to 1.86)	1.25 (0.93 to 1.70)
P_{trend}§		<.001	.007	P_{trend}§		.02	.14
BMI, kg/m^2				BMI, kg/m^2			
<23.6	64	1 (Referent)	1 (Referent)	<21.7	87	1 (Referent)	1 (Referent)
23.6–25.3	85	1.20 (0.86 to 1.66)	1.18 (0.85 to 1.63)	21.7–23.5	96	0.92 (0.69 to 1.23)	0.92 (0.68 to 1.23)
25.4–27.0	74	1.03 (0.74 to 1.45)	1.00 (0.71 to 1.41)	23.6–25.7	120	1.02 (0.77 to 1.35)	1.02 (0.77 to 1.35)
27.1–29.3	88	1.24 (0.89 to 1.72)	1.19 (0.85 to 1.66)	25.8–28.8	137	1.09 (0.83 to 1.44)	1.09 (0.83 to 1.45)
≥29.4	110	1.64 (1.19 to 2.25)	1.55 (1.12 to 2.15)	≥28.9	123	1.04 (0.78 to 1.39)	1.06 (0.79 to 1.42)
P_{trend}§		.002	.006	P_{trend}§		.46	.40

*Number of colon cancer patients. BMI = body mass index; WHR = waist-to-hip ratio.

†Crude model is derived from Cox regression using age as the underlying time variable and stratified by center and age at recruitment.

‡Multivariable models for height and BMI were based on the crude model with additional adjustment for smoking status (never, past, current, or unknown), education (no school degree or primary school, technical or professional school, secondary school, university degree, or unknown), alcohol intake (continuous), physical activity (inactive, moderately inactive, moderately active, active, or missing), fiber intake (continuous), and consumption of red and processed meat (continuous), fish and shellfish (continuous), and fruits and vegetables (continuous). Multivariable model for weight, waist, hip, and WHR were further adjusted for height (continuous).

§P_{trend} (two-sided) across categories is based on the median anthropometric variable within quintiles as a continuous variable and was calculated using the Wald chi-square statistic.

(segue) Indici antropometrici e rischio di CCR
EPIC Europa (Pischon et al, 2006)

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Men				Women			
Measure	N*	Crude RR (95% CI)†	Multivariable RR (95% CI)‡	Measure	N*	Crude RR (95% CI)†	Multivariable RR (95% CI)‡
Waist circumference, cm				Waist circumference, cm			
<86.0	63	1 (Referent)	1 (Referent)	<70.2	62	1 (Referent)	1 (Referent)
86.0–91.8	57	0.75 (0.53 to 1.08)	0.73 (0.50 to 1.04)	70.2–75.8	91	1.13 (0.81 to 1.56)	1.10 (0.80 to 1.52)
91.9–96.5	78	1.03 (0.74 to 1.44)	0.97 (0.69 to 1.36)	75.9–80.9	125	1.27 (0.93 to 1.73)	1.23 (0.90 to 1.68)
96.6–102.9	95	1.20 (0.87 to 1.66)	1.10 (0.79 to 1.53)	81.0–88.9	135	1.29 (0.95 to 1.76)	1.25 (0.91 to 1.70)
≥103.0	125	1.56 (1.14 to 2.14)	1.39 (1.01 to 1.93)	≥89.0	149	1.53 (1.12 to 2.09)	1.48 (1.08 to 2.03)
P_{trend}§		<.001	.001	P_{trend}§		.004	.008
Hip circumference, cm				Hip circumference, cm			
<95.2	71	1 (Referent)	1 (Referent)	<93.7	83	1 (Referent)	1 (Referent)
95.2–98.9	62	0.93 (0.66 to 1.31)	0.90 (0.64 to 1.27)	93.7–97.9	90	1.03 (0.76 to 1.39)	0.99 (0.73 to 1.34)
99.0–101.9	97	1.13 (0.83 to 1.55)	1.08 (0.78 to 1.48)	98.0–101.9	137	1.16 (0.88 to 1.52)	1.09 (0.82 to 1.44)
102.0–105.9	76	1.36 (0.98 to 1.89)	1.27 (0.90 to 1.78)	102.0–107.9	108	1.10 (0.82 to 1.47)	1.02 (0.76 to 1.38)
≥106.0	110	1.51 (1.11 to 2.06)	1.37 (0.99 to 1.90)	≥108.0	142	1.28 (0.97 to 1.70)	1.20 (0.89 to 1.60)
P_{trend}§		<.001	.01	P_{trend}§		.07	.19
WHR				WHR			
<0.887	48	1 (Referent)	1 (Referent)	<0.734	68	1 (Referent)	1 (Referent)
0.887–0.922	72	1.19 (0.83 to 1.72)	1.16 (0.80 to 1.68)	0.734–0.768	94	1.06 (0.78 to 1.46)	1.07 (0.78 to 1.47)
0.923–0.952	77	1.19 (0.83 to 1.72)	1.15 (0.79 to 1.65)	0.769–0.802	113	1.13 (0.83 to 1.53)	1.15 (0.84 to 1.56)
0.953–0.989	109	1.63 (1.15 to 2.31)	1.54 (1.08 to 2.19)	0.803–0.845	125	1.17 (0.86 to 1.58)	1.19 (0.88 to 1.61)
≥0.990	110	1.63 (1.15 to 2.31)	1.51 (1.06 to 2.15)	≥0.846	160	1.48 (1.10 to 2.00)	1.52 (1.12 to 2.05)
P_{trend}§		<.001	.006	P_{trend}§		.003	.002

*Number of colon cancer patients. BMI = body mass index; WHR = waist-to-hip ratio.

†Crude model is derived from Cox regression using age as the underlying time variable and stratified by center and age at recruitment.

‡Multivariable models for height and BMI were based on the crude model with additional adjustment for smoking status (never, past, current, or unknown), education (no school degree or primary school, technical or professional school, secondary school, university degree, or unknown), alcohol intake (continuous), physical activity (inactive, moderately inactive, moderately active, active, or missing), fiber intake (continuous), and consumption of red and processed meat (continuous), fish and shellfish (continuous), and fruits and vegetables (continuous). Multivariable model for weight, waist, hip, and WHR were further adjusted for height (continuous).

§P_{trend} (two-sided) across categories is based on the median anthropometric variable within quintiles as a continuous variable and was calculated using the Wald chi-square statistic.

ATTIVITA' FISICA

- Numerosi studi hanno evidenziato un **effetto protettivo dell'attività fisica** sul tumore del colon indipendentemente dal BMI.
- I dati sul tumore del retto sono meno consistenti.
- Livelli crescenti (per intensità, frequenza e durata) di attività si accompagnano ad una maggiore riduzione del rischio.
- Si stima che circa il 13-14% dei tumori del colon sia attribuibile alla inattività fisica.
- Un effetto protettivo consistente è stato stimato a partire da 30 minuti giornalieri di attività di intensità abbastanza elevata.
- Un'attività fisica regolare si associa, nello stesso studio, con una riduzione del rischio di circa il 30% per i tumori del colon, riduzione che raggiunge il 70% per i tumori del colon destro nei soggetti con BMI normale. Friedenreich C, Riboli E, et al., Cancer Epidemiol Biomarkers Prev 2006 Dec 15(12): 2398-4

CONCLUSIONI

- Il ruolo di un'alimentazione corretta, dell'attività fisica e del controllo del peso corporeo nella prevenzione dei tumori è oggi scientificamente documentato. Sono disponibili anche studi collaborativi condotti nella popolazione italiana.

- Gli studi prospettici (coorti) di grandi dimensioni svolgono un ruolo fondamentale per identificare le cause di tumore legate a stili di vita ed ambientali complesse (ed altre patologie croniche o condizioni quali l'obesità, il diabete, patologie cardio-vascolari…).

- Un'accurata pianificazione dello stoccaggio dei campioni, assieme alla raccolta di informazioni individuali dettagliate comporta una preziosa opportunità di individuare i fattori metabolici in relazione al rischio di tumore.

- I campioni raccolti negli studi prospettici sono essenziali per escludere il fenomeno della causalità inversa (*reverse-causation*)

- Risultati attendibili sono fondamentali per sviluppare raccomandazioni e linee guida per una dieta corretta.

CONCLUSIONI

- L'evidenza disponibile per quanto riguarda i principali fattori di rischio e protettivi per il tumore della mammella e del colon-retto appare sufficiente per il trasferimento nella pratica operativa e per l'avvio di campagne mirate di **prevenzione primaria**.

- Il controllo del peso, l'aumento dell'attività fisica e una dieta ricca di frutta e verdura ed altri alimenti ricchi di fibra e poveri di grassi animali sono importanti anche per la prevenzione di altre patologie croniche.

- Restano da **definire le strategie** più adatte per modificare in modo permanente le abitudini alimentari e lo stile di vita nella popolazione generale o in sottogruppi a rischio.

- Gli studi randomizzati di intervento rappresentano uno strumento insostituibile per la valutazione dell'efficacia delle varie strategie.