

## Obesity and cancer

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The first of the 10 Recommendations for cancer prevention listed in the 2<sup>nd</sup> Report *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a global perspective* published by the World Cancer Research Fund (WCRF) was “Be lean as possible within the normal range of body weight”.

More recently the importance of weight control has been reaffirmed in the European Code against Cancer<sup>1</sup>.

Systematic evaluations of a large number of studies, carried out in different countries and populations, and at several sites, have reported consistently that excess body fat is associated with an increased cancer risk<sup>2</sup>. Most of the evidence derives from prospective studies, such as the European Prospective Investigation into Cancer and Nutrition (EPIC), a multicenter study coordinated by the International Agency of Research on Cancer (IARC) including 500.000 healthy adults (over 47.000 residing in Italy), for which information at enrolment (1993-1997) on diet and lifestyle, a blood sample and a series of anthropometric measures were obtained by trained nurses and made available.

Several studies have shown a positive association between body mass index (BMI), central obesity and weight gain in adulthood and the risk for colorectal cancer. The risk appears higher for the colon localization. Very interestingly an analysis carried out in the EPIC study, based on more than 380,000 subjects and 1700 cancer cases identified in a follow up of six years, showed a positive association between weight, waist and hip circumference and colorectal cancer risk among males, while in women only the central obesity indices were associated with the risk – thus suggesting a more relevant role of central adiposity in the development of this neoplasm<sup>3</sup>.

For other gastrointestinal sites, specifically oesophageal adenocarcinoma, cardia, pancreas, liver and gallbladder cancer, a positive association between increased BMI and risk was reported in many studies. Stratification, when available, showed a similar increase in risk of these neoplasms in both males and females.

A recent systematic review of available epidemiological studies, carried out by the WCRF Continuous Updated Project in 2017, concludes that there is “convincing evidence” that being overweight/obese (high BMI, waist and hip circumference, waist-hip ratio) or to

experience a significant weight gain in adulthood increases postmenopausal breast cancer risk. On the contrary, a probable decrease in risk emerges in studies evaluating the association between BMI and premenopausal breast cancer, while data on associations with central adiposity indices are less consistent. The reasons for these differences are still unclear. Sex steroid hormones, including oestrogens, androgens and progesterone, are likely to play a relevant role in the association between obesity and breast cancer development. Indeed, after menopause, adipose tissue is the major source of endogenous oestrogen while abnormal hormone profiles associated with obesity could be related to the inverse association between obesity and breast cancer in young women. High values of BMI and other anthropometric indices (waist and hip circumference) are associated with increased risk of endometrial cancer. High BMI at a young age and adult weight gain are also risk factors for this neoplasm. The risk related to adiposity is higher in postmenopause and in women not using hormone therapy. In recent years numerous prospective studies have also shown a positive association between elevated BMI and ovary cancer<sup>4</sup>.

Finally, there is also an increasing evidence supporting an association between increased BMI near the time of the diagnosis and weight gain after diagnosis and reduced survival in breast cancer patients. Data on other cancer survivors is sparse and less consistent.

Mechanisms that have been hypothesized to mediate the association between obesity and cancer include alterations in sex hormone metabolism, insulin and insulin-like growth factor (IGF) signalling and adipokines or inflammatory pathways.

Moreover some studies have shown that an intentional weight loss in adulthood can affect positively the association between adiposity and cancer. Recently a study carried out in a Women’s Health Initiative (WHI) observational study showed that intentional weight loss ( $\geq 5\%$ ) was associated with a lower risk of endometrial cancer, especially among obese women<sup>5</sup>.

Obesity is an established risk factor for chronic diseases including cancer and its prevalence is increasing, therefore the prevention of weight gain throughout a person’s life is a public health goal.

Large prospective studies have contributed to the investigation of lifestyle and dietary determinants of weight change in adulthood. In the Diogenes Project, an European program aimed at targeting the obesity problem from a dietary perspective, 5 EPIC Cohorts (Cambridge – UK; Aarhus/Copenhagen – DK; Potsdam – D; Bilthoven – NL and Florence – I) accounting for over 90,000 subjects with repeated anthropometric measures were involved. The main results of specific analyses aimed at investigating the association between dietary habits at enrolment and subsequent weight changes, showed that as the consumption of fruit and vegetables increases, the weight increase is reduced<sup>6</sup>. A food pattern characterized by high consumption of fruit and dairy products, reduced consumption of white bread, preserved meat, margarine, sugary drinks foods with high glycemic index and high energy density are associated with a lower accumulation of abdominal fat<sup>7,8</sup>. High intake of dietary fibre, in particular from cereals, was associated with lower weight and waist circumference gain<sup>9</sup>. A positive association between the high consumption of total proteins and in particular of proteins of animal origin and weight gain in both sexes and in particular in women also emerged. The association seems to be attributed to the proteins of fresh and preserved red meat and poultry, but not to fish and dairy products. There is no association with proteins of plant origin<sup>10</sup>.

Similar results were obtained in other large prospective cohorts carried out in the United States<sup>11</sup>.

In conclusion, the role of being overweight and obesity in increasing the risk of a series of cancers including colorectal cancer, and the main female tumours (postmenopausal breast and endometrium) is now scientifically documented. For some tumours there is also evidence of a risk related to weight gain in adulthood. A series of plausible mechanisms have been hypothesized that may explain this relationship between obesity and cancer risk.

Weight control along with increased physical activity, a diet rich in vegetables and other foods rich in fibre and low in animal fats seems to be useful in preventing weight gain and are also important for the prevention of chronic diseases. The most suitable strategies to modify food habits and lifestyle in the general population or in subgroups at risk and in “critical” periods such as menopausal transition in women, and to allow a long-term weight control are not yet clearly defined. Randomized intervention studies are needed for evaluating the effectiveness of various strategies.

## References

- Schüz J, Espina C, Villain P, Herrero R, Leon ME, Minozzi S, et al. European code against Cancer 4th Edition: 12 ways to reduce your cancer risk. *Cancer Epidemiol* 2015; 39 (Suppl 1): S1-10.
- Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K, International Agency for Research on Cancer Handbook Working Group. Body fatness and cancer-viewpoint of the IARC Working Group. *N Engl J Med* 2016; 375 (8): 794-8.
- Pischoon T, Lahmann PH, Boeing H, Friedenreich C, Norat T, Tjønneland A, et al. Body size and risk of colon and rectal cancer in the European Prospective. Investigation Into Cancer and Nutrition (EPIC). *J Natl Cancer Inst* 2006; 98 (13): 920-31.
- Aune D, Navarro Rosenblatt DA, Chan DS, Abar L, Vingeliene S, Vieira AR, et al. Anthropometric factors and ovarian cancer risk: a systematic review and nonlinear dose-response meta-analysis of prospective studies. *Int J Cancer* 2015; 136 (8): 1888-98.
- Luo J, Chlebowski RT, Hendryx M, Rohan T, Wactawski-Wende J, Thomson CA, et al. Intentional weight loss and endometrial cancer risk. *J Clin Oncol* 2017; 35 (11): 1189-93.
- Buijsse B, Feskens EJ, Schulze MB, Forouhi NG, Wareham NJ, Sharp S, et al. Fruit and vegetable intakes and subsequent changes in body weight in European populations: results from the project on diet, obesity, and genes (DiO-Genes). *Am J Clin Nutr* 2009; 90 (1): 202-9.
- Romaguera D, Angquist L, Du H, Jakobsen MU, Forouhi NG, Halkjaer J, et al. Dietary determinants of changes in waist circumference adjusted for body mass index – a proxy measure of visceral adiposity. *PLoS One* 2010; 5 (7): e11588.
- Romaguera D, Angquist L, Du H, Jakobsen MU, Forouhi NG, Halkjaer J, et al. Food composition of the diet in relation to changes in waist circumference adjusted for body mass index. *PLoS One* 2011; 6 (8): e23384.
- Du H, van der A DL, Boshuizen HC, Forouhi NG, Wareham NJ, Halkjaer J, et al. Dietary fiber and subsequent changes in body weight and waist circumference in European men and women. *Am J Clin Nutr* 2010; 91 (2): 329-36.
- Halkjaer J, Olsen A, Overvad K, Jakobsen MU, Boeing H, Buijsse B, et al. Intake of total, animal and plant protein and subsequent changes in weight or waist circumference in European men and women: the Diogenes project. *Int J Obes (Lond)* 2011; 35 (8): 1104-13.
- Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB. Changes in diet and lifestyle and long-term weight gain in women and men. *N Engl J Med* 2011; 364 (25): 2392-404.

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