Body Fatness and Cancer — Viewpoint of the IARC Working Group

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In April 2016, the International Agency for Research on Cancer (IARC), based in Lyon, France, convened a working group to reassess the preventive effects of weight control on cancer risk. (The members of the working group for volume 16 of the IARC Handbooks are listed at the end of the article; affiliations are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.) Overweight and obesity are the abnormal or excessive accumulation of body fat that present a risk to health. The body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) is a good proxy for assessing overall body fatness. Among adults, overweight is defined as a BMI of 25.0 to 29.9 and obesity as a BMI of 30 or more.[1] Obesity can further be divided into class 1 (BMI, 30.0 to 34.9), class 2 (BMI, 35.0 to 39.9), and class 3 (BMI, ≥40.0) (Table 1).

Worldwide, an estimated 640 million adults in 2014 (an increase by a factor of 6 since 1975) and 110 million children and adolescents in 2013 (an increase by a factor of 2 since 1980) were obese. The estimated age-standardized prevalence of obesity in 2014 was 10.8% among men, 14.9% among women,[2] and 5.0% among children,[3] and globally more people are overweight or obese than are underweight.

In 2013, an estimated 4.5 million deaths worldwide were caused by overweight and obesity; on the basis of recent estimates, the obesity-related cancer burden represents up to 9% of the cancer burden among women in North America, Europe, and the Middle East.[4] Body fatness and weight gain throughout the life course are largely determined by modifiable risk factors, such as excess energy intake (food and drink) and (to a lesser extent) physical inactivity, which are the main drivers of the obesity epidemic. In 2002, the previous IARC working group concluded that there was sufficient evidence for a cancer-preventive effect of avoidance of weight gain for cancers of the colon, esophagus (adenocarcinoma), kidney (renal-cell), breast (postmenopausal), and corpus uteri.[5]

EPIDEMIOLOGIC STUDIES

For the current reassessment, most of the more than 1000 epidemiologic studies that we reviewed were observational studies on cancer risk and excess body fatness, because studies, including clinical trials, of weight-loss or weight-control interventions were sparse. Consequently, the evaluations were based on increased risks associated with excess body fatness rather than reduced risks associated with preventive interventions. Most studies provided risk estimates for adult BMI, whereas some provided estimates for BMI or body shape in childhood or adolescence, changes in BMI or weight over time, or other indicators of adiposity, such as waist circumference. When adequate meta-analyses of observational studies were available, we also took relative-risk estimates into account. Most relative risks are provided relative to a BMI of 18.5 to 24.9.

On the basis of these data, we termed the attribute "excess body fatness" and reaffirmed that

Table 1. Definitions of Classes of Overweight and Obesity.

Class	Body-Mass Index
Overweight	25.0–29.9
Obesity	
Class 1	30.0–34.9
Class 2	35.0–39.9
Class 3	≥40.0

the absence of excess body fatness lowers the risk of cancer at the organ sites that have been identified previously (Table 2). Furthermore, we identified an additional eight cancers for which there is now also sufficient evidence that the absence of body fatness lowers cancer risk, including cancers of the gastric cardia, liver, gallbladder, pancreas, ovary, and thyroid, as well as multiple myeloma and meningioma. (For detailed information on the evaluation criteria, see the working procedures section of the IARC Handbooks of Cancer Prevention website at http://handbooks .iarc.fr/workingprocedures/index1.php.)

For cancers of the colon, rectum, gastric cardia, liver, gallbladder, pancreas, and kidney and for esophageal adenocarcinoma, significant associations between BMI and cancer risk were reported, with positive dose–response relationships. Relative risks from meta-analyses or pooled analyses were 1.2 to 1.5 for overweight and 1.5 to 1.8 for obesity with respect to cancers of the colon,[6,7] gastric cardia,[8] liver,[9] gallbladder,[10] pancreas,[11] and kidney[12]; the relative risk for esophageal adenocarcinoma was up to 4.8 for a BMI of 40 or more.[13] Results that were based on waist circumference were generally consistent with those reported for BMI. When studies from different geographic regions were available (for cancers of the colon, gastric cardia, and liver, as well as esophageal adenocarcinoma), the results were consistent across regions.[14] Stratification according to sex, when available, generally showed similarly increased risks among men and women. Studies of mendelian randomization (which involve assigning people to groups on the basis of genotypic variation that may be associated with a particular risk factor) allow leveraging the properties of genetic variation to overcome potential limitations present in observational epidemiologic studies. Results from such studies on cancer of the colorectum[15] and esophageal adenocarcinoma[16] were in agreement with those from cohort and case–control studies.

Positive associations have been observed between adult BMI and postmenopausal breast cancer in numerous studies (relative risk, approximately 1.1 per 5 BMI units),[6] particularly for estrogen-receptor–positive tumors. Waist circumference and body-weight gain in adulthood were also positively associated with the risk of postmenopausal breast cancer. For premenopausal breast cancer, consistent inverse associations have been observed between BMI and risk.[6] However, data on associations with waist circumference or body-weight gain were inconsistent. These differences remain not fully explained.

The association between BMI and endometrial cancer was particularly pronounced for type 1 endometrial cancer. There was a strong dose–response relationship, with relative risks of approximately 1.5 for overweight, 2.5 for class 1 obesity, 4.5 for class 2 obesity, and 7.1 for class 3 obesity.[17] A modest positive association was observed for epithelial ovarian cancer, with a relative risk of 1.1.[18] Results from studies that used mendelian randomization were consistent with these findings.[19] Among women who had received hormone-replacement therapy, the strength of the association with excess body fatness was reduced for endometrial cancer,[20] and no association was observed for ovarian cancer[18] or postmenopausal breast cancer.[21]

For multiple myeloma, the available data showed positive associations with adult BMI, with relative risks of approximately 1.2 for overweight, 1.2 for class 1 obesity, and 1.5 for class 2 or 3 obesity.[22] On the basis of several cohort or case–control studies, a positive association was observed between BMI and the risk of meningioma[23] and thyroid cancer.[24] In addition to the cancer sites for which there was sufficient evidence, we concluded that there is limited evidence for an association between excess body fatness and fatal prostate cancer,[25] diffuse large B-cell lymphoma,[26] and male breast cancer.[27]

We reviewed studies of eight other cancers for which the evidence for an association was considered inadequate, owing to limited data, inconsistent results, or no data suggesting an association: cancers of the lung, esophagus (squamous-cell carcinoma), gastric noncardia, extrahepatic biliary tract, skin (cutaneous melanoma), testis, urinary bladder, and brain or spinal cord (glioma).

In addition, we reviewed data pertaining to BMI in childhood, adolescence, and young adulthood (≤25 years of age) to assess whether increased BMI at these ages is linked with cancer in adult life. Positive associations were reported for several cancers also known to be associated with increased adult BMI, with the notable exception of postmenopausal breast cancer. The associations were generally similar to those with adult BMI, despite some differences in magnitude and patterns.

Table 2. Strength of the Evidence for a Cancer-Preventive Effect of the Absence of Excess Body Fatness, According to Cancer Site or Type.*

Cancer Site or Type	Strength of the Evidence in Humans†	Relative Risk of the Highest BMI Category Evaluated versus Normal BMI (95% CI)‡
Esophagus: adenocarcinoma	Sufficient	4.8 (3.0–7.7)
Gastric cardia	Sufficient	1.8 (1.3–2.5)
Colon and rectum	Sufficient	1.3 (1.3–1.4)
Liver	Sufficient	1.8 (1.6–2.1)
Gallbladder	Sufficient	1.3 (1.2–1.4)
Pancreas	Sufficient	1.5 (1.2–1.8)
Breast: postmenopausal	Sufficient	1.1 (1.1–1.2)§
Corpus uteri	Sufficient	7.1 (6.3–8.1)
Ovary	Sufficient	1.1 (1.1–1.2)
Kidney: renal-cell	Sufficient	1.8 (1.7–1.9)
Meningioma	Sufficient	1.5 (1.3–1.8)
Thyroid	Sufficient	1.1 (1.0–1.1)§
Multiple myeloma	Sufficient	1.5 (1.2–2.0)
Male breast cancer	Limited	NA
Fatal prostate cancer	Limited	NA
Diffuse large B-cell lymphoma	Limited	NA
Esophagus: squamous-cell carcinoma	Inadequate	NA
Gastric noncardia	Inadequate	NA
Extrahepatic biliary tract	Inadequate	NA
Lung	Inadequate	NA
Skin: cutaneous melanoma	Inadequate	NA
Testis	Inadequate	NA
Urinary bladder	Inadequate	NA
Brain or spinal cord: glioma	Inadequate	NA

* BMI denotes body-mass index, CI confidence interval, and NA not applicable.
† Sufficient evidence indicates that the International Agency for Research on Cancer Handbook Working Group considers that a preventive relationship has been established between the intervention (in this case, the absence of excess body fatness) and the risk of cancer in humans — that is, a preventive association has been observed in studies in which chance, bias, and confounding could be ruled out with confidence. Limited evidence indicates that a reduced risk of cancer is associated with the intervention for which a preventive effect is considered credible by the working group, but chance, bias, or confounding could not be ruled out with confidence. Inadequate evidence indicates that the available studies are not of sufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of a cancer-preventive effect of the intervention or that no data on the prevention of cancer by this intervention in humans are available. Additional information on the criteria for classification of the evidence is available at http://handbooks.iarc.fr/docs/Handbook16_Working-Procedures.PrimaryPrevention.pdf.
‡ For cancer sites with sufficient evidence, the relative risk reported in the most recent or comprehensive meta-analysis or pooled analysis is presented. The evaluation in the previous column is based on the entire body of data available at the time of the meeting (April 5–12, 2016) and reviewed by the working group and not solely on the relative risk presented in this column. Normal BMI is defined as 18.5 to 24.9.
§ Shown is the relative risk per 5 BMI units.

We assessed reviews of the association between body fatness on cancer recurrence and survival after diagnosis and noted considerable variation in study design, setting, and timing of body-fatness measurement relative to cancer diagnosis. There was a large volume of evidence supporting an association between increased BMI near the time of cancer diagnosis and reduced survival in patients with breast cancer, whereas evidence for other cancers was sparse and less consistent. One

intervention trial, in which a low-fat diet intervention led to modest weight loss, resulted in a reduction in breast-cancer recurrence.[28]

Data on body-weight loss, either from observational studies[21] or from follow-up of patients undergoing bariatric surgery,[29] suggested that intentional weight loss may reduce cancer risk, notably for breast and endometrial cancer. However, the number and quality of these studies were judged to be insufficient for a formal evaluation.

STUDIES IN EXPERIMENTAL ANIMALS

Numerous models in experimental animals have been used to study the association between obesity and cancer at various organ sites. Overall, the data showed that obesity in rodents promotes tumorigenesis and increases the age-specific incidence of cancers of the mammary gland, colon, liver, pancreas, prostate (advanced stage), and skin, as well as, to a lesser extent, leukemia.[30,31]

Similarly, a large number of studies in several rodent models evaluated associations between caloric or dietary restriction, which limits body-weight gain in comparison with controls fed ad libitum, and the prevention of tumor development or progression. We concluded that there is sufficient evidence in experimental animals for a cancer-preventive effect of limitation of body-weight gain by caloric or dietary restriction for cancers of the mammary gland, colon, liver, pancreas, skin, and pituitary gland. In addition, an inverse association was observed between caloric or dietary restriction and cancer of the prostate, lymphoma, and leukemia.

MECHANISTIC DATA

We identified which cellular and molecular mechanisms that are known to be altered during carcinogenesis[32,33] could be causally linked with obesity, and we evaluated the relevance of each mechanism for cancer overall and for specific organ sites when sufficient data were available. Obesity is associated with substantial metabolic and endocrine abnormalities, including alterations in sex hormone metabolism, insulin and insulin-like growth factor (IGF) signaling, and adipokines or inflammatory pathways.[34,35] Evidence for a role of sex hormone metabolism and of chronic inflammation in mediating the obesity–cancer relation is strong, and evidence for a role of insulin and IGF signaling is moderate. In addition, there was convincing evidence that intentional body-weight loss positively affects these mechanisms. The beneficial effects on cancer risk appear to be mediated, at least in part, by regulation of the balance between cell proliferation and apoptosis,[36] known determinants in carcinogenesis.

EVALUATION AND CONCLUSIONS

On the basis of the available data, we concluded that the absence of excess body fatness lowers the risk of most cancers. In addition, a review of studies in experimental animals and mechanistic data suggest a causal cancer-preventive effect of intentional weight loss, although evidence in humans remains to be established.

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