REVIEW

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Beyond cardiovascular risk: The impact of obesity on cancer death

ABSTRACT

Obesity is associated with higher rates of death due to cancer. Possible explanations for this association include physiological factors associated with obesity, lower cancer screening rates in obese people, and technical difficulties in treating obese patients. These problems represent opportunities to improve the care of obese patients.

KEY POINTS

Obese people have higher rates of death from many (but not all) types of cancer. For people with a body mass index (BMI) of 40 kg/m^2 or greater, the relative risk of dying of any type of cancer is 1.52 for men and 1.62 for women, compared with people of normal weight (BMI 18.5–24.9 kg/m^2).

Obesity may directly cause cancer via the effects of insulin, unbound insulin-like growth factor-1, inflammation, and circulating levels of female sex hormones.

Cancer screening rates are lower among obese patients, for several reasons: more attention is paid to comorbid conditions, obese patients tend to be of lower socioeconomic status, screening can involve more technical difficulties, and obese patients are more likely to avoid screening tests.

In obese people, cancer treatment is complicated by increased surgical difficulties as well as uncertainty in chemotherapy and radiotherapy dosing.

COMPLETE THIS SENTENCE: People who are obese have an increased risk of dying of . . .

You probably said "cardiovascular disease," and you would be correct. But obesity is also linked to death from cancer, an association that receives far less attention—and deserves more attention than it gets. Cancer is the second leading cause of death in the United States, and by some estimates, obesity might account for 14% of cancer deaths in men and 20% in women. And as obesity rates rise, obesity-related health problems of all types are escalating.

In this review, we summarize the evidence supporting a link between obesity and increased cancer incidence and mortality, discuss possible explanations, and recommend ways to enhance cancer prevention.

OBESITY IMPOSES A PUBLIC HEALTH BURDEN

More than 65% of adults in the United States are either overweight (body mass index [BMI] 25–29.9 kg/m^2) or obese (BMI ≥ 30 kg/m^2).[1] Attempts to reduce these rates have been largely unsuccessful.

Obesity imposes an estimated $117 billion annually in direct and indirect health care costs.[2] The number of deaths attributable to obesity is unknown, but estimates range from 112,000 to 365,000 per year.[3,4]

Obesity is an important risk factor for cardiovascular disease, the leading cause of death in the United States. Mechanisms include impaired glucose tolerance, hypertension, and hyperlipidemia.[5,6] Other important conditions associated with obesity include atrial fibrillation, obstructive sleep apnea, asthma, depres-

TABLE 1

Cancer Prevention Study II: Cancer mortality risk in obese men

CANCER TYPE	BMI (KG/M²)	ADJUSTED RELATIVE RISK*	95% CONFIDENCE INTERVAL
Liver	≥ 35	4.52	2.94–6.94
Pancreas†	≥ 35	2.61	1.27–5.35
Stomach	≥ 35	1.94	1.21–3.13
Esophagus†	≥ 30	1.91	0.92–3.96
Colorectal	≥ 35	1.84	1.39–2.41
Gallbladder	≥ 30	1.76	1.06–2.94
Multiple myeloma	≥ 35	1.71	0.93–3.14
Kidney	≥ 35	1.70	0.99–2.92
Leukemia	≥ 35	1.70	1.08–2.66
Non-Hodgkin lymphoma	≥ 35	1.49	0.93–2.39
Prostate	≥ 35	1.34	0.98–1.83
Lung	≥ 35	0.67	0.54–0.84
All cancers	≥ 40	1.52	1.13–2.05

BMI, body mass index.
*Compared with men with BMI 18.5 to 24.9. All calculations are adjusted for age, education, smoking status and number of cigarettes smoked, physical activity, alcohol use, marital status, race, aspirin use, fat consumption, and vegetable consumption. For all cancers above, trends in relative risks were statistically significant ($P < .05$) across all BMI groups, but some of the confidence intervals overlapped 1.0 for the highest BMI group based on sample size.
†Risk in men who never smoked.

sion, gallbladder disease, and osteoarthritis.[7–10] And an association with many types of cancer has been observed for decades.[11]

OBESITY AND CANCER DEATH: THE CANCER PREVENTION STUDY II

In 2003, Calle et al[12] reported the results of the Cancer Prevention Study II, in which more than 900,000 people in the United States were prospectively followed for 16 years. The average age at enrollment was 57 years, and baseline data included race, sex, dietary patterns, smoking status, weight, and height. People with known or suspected cancer were excluded.

The cause of death was determined for 98.8% of the people who died; approximately 57,000 people died of cancer. People with a higher BMI had a higher risk of death from many of the most common types of cancer, including colorectal, postmenopausal breast, prostate, pancreatic, and ovarian cancer (**TABLE 1, TABLE 2**). For unknown reasons, the lung cancer mortality rate was lower in obese men and women, particularly among those who smoked.

The heaviest men (BMI ≥ 40 kg/m²) had a 52% higher rate of cancer death than men of normal weight (BMI 18.5–24.9 kg/m²) after adjustment for confounding variables such as age, education, physical activity, cigarette smoking, alcohol use, marital status, race, aspirin use, and fat and vegetable consumption. The higher mortality rate in men was most striking in cancers of the digestive system, particularly pancreatic and hepatic cancers.

Similarly, the heaviest women had a 62% higher risk of cancer death after adjustment for the same variables in addition to estrogen replacement therapy. The increased risk in women was greatest for cancers of the reproductive system, breast (after menopause), and kidney.

The investigators estimated that, based on their findings, about 14% of cancer deaths in men and 20% of cancer deaths in women are attributable to being overweight or obese, which equals approximately 90,000 preventable cancer deaths each year.

Other studies had similar findings.[13,14]

THREE PLAUSIBLE MECHANISMS OF INCREASED RISK

Three mechanisms might explain the increased risk of dying of cancer seen in obese people:

- Obesity may cause cancer
- Obese people may be screened for cancer less often, and therefore their disease is diagnosed at a later stage
- Obese patients diagnosed with cancer may have worse outcomes because of factors related to obesity.

There is evidence to support each of these mechanisms, indicating that the phenomenon may be multifactorial (**FIGURE 1**).

Obesity may be carcinogenic

Increased insulin. Growing evidence indicates that insulin resistance, a metabolic complication of obesity, may promote not only type 2 diabetes but also cancer. Epidemiologic studies have shown that chronic hyperinsulinemia and hyperglycemia are associated with several types of cancer, and the relationship persists after controlling for BMI.[15,16]

Insulin influences cell growth and inflammation in several ways. For instance, it promotes the production of insulin-like growth factor (IGF-1), and in laboratory studies, insulin and IGF-1 stimulate cell proliferation and inhibit apoptosis (programmed cell death).[17] Although obese people have low normal serum levels of total IGF-1, they have high levels of the unbound molecule (the biologically active form),[18,19] which could promote cancer development.[15] People with acromegaly—who have elevated levels of unbound IGF-1—have an increased risk of colorectal, postmenopausal breast, and hematologic cancers.[20]

Increased inflammation. Adipose tissue is an important source of inflammatory mediators, free fatty acids, and other metabolically active products known as adipokines, which include leptin, tumor necrosis factor alpha, interleukin 6, and adiponectin.[21] Inflammation is associated with cancer risk, possibly by generating reactive oxygen species that could damage DNA.[15]

Higher estrogen levels. Obesity may promote cancer via elevated levels of circulating female sex hormones. Obese women have higher levels of circulating estrogens, which are thought to be generated through the increased activity of aromatase in adipose tissues and lower levels of sex-hormone-binding globulin.[22] Evidence of the link between increased estrogen levels and cancer is that endometrial cancer rates are higher in postmenopausal women who are given unopposed estrogen. Also, postmenopausal breast cancer rates are higher in women who received hormone replacement therapy.[23,24]

Obese people are screened less often

Rosen and Schneider[25] found that morbidly obese women are less likely than other groups to be screened for colorectal cancer, a disease that often can be prevented with appropriate screening and early treatment.

Similarly, Wee et al,[26] in a secondary data analysis of the Year 2000 Supplement of the National Health Interview Survey, found that 22% of obese women ages 18 to 75 years failed to undergo Papanicolaou (Pap) smears in the previous 3 years, compared with 16% of their normal-weight peers. In addition, 38% of obese women ages 50 to 75 years failed to undergo mammography in the preceding 2 years, compared with 32% of their normal-weight peers. These differences were statistically significant and persisted after controlling for socioeconomic status, insurance status, illness burden, and provider specialty. The dis-

TABLE 2

Cancer Prevention Study II: Cancer mortality risk in obese women

CANCER TYPE	BMI (KG/M²)	ADJUSTED RELATIVE RISK*	95% CONFIDENCE INTERVAL
Uterus	≥ 40	6.25	3.75–10.42
Kidney	≥ 40	4.75	2.50–9.04
Cervix	≥ 35	3.20	1.77–5.78
Pancreas	≥ 40	2.76	1.74–4.36
Esophagus†	≥ 30	2.64	1.36–5.12
Gallbladder	≥ 30	2.13	1.56–2.90
Breast (postmenopausal)	≥ 40	2.12	1.41–3.19
Non-Hodgkin lymphoma	≥ 35	1.95	1.39–2.72
Liver	≥ 35	1.68	0.93–3.05
Ovary	≥ 35	1.51	1.12–2.02
Colorectal	≥ 40	1.46	0.94–2.24
Multiple myeloma	≥ 35	1.44	0.91–2.28
Lung	≥ 40	0.81	0.52–1.28
All cancers	≥ 40	1.62	1.40–1.87

BMI, body mass index.
*Compared with women with BMI 18.5–24.9. All calculations are adjusted for age, education, smoking status and number of cigarettes smoked, physical activity, alcohol use, marital status, race, aspirin use, fat consumption, and vegetable consumption. For all cancers above, trends in relative risks were statistically significant ($P < .05$) across all BMI groups, but some of the confidence intervals overlapped 1.0 for the highest BMI group based on sample size.
†Risk in women who never smoked.

Possible mechanisms for the relationship between obesity and cancer death

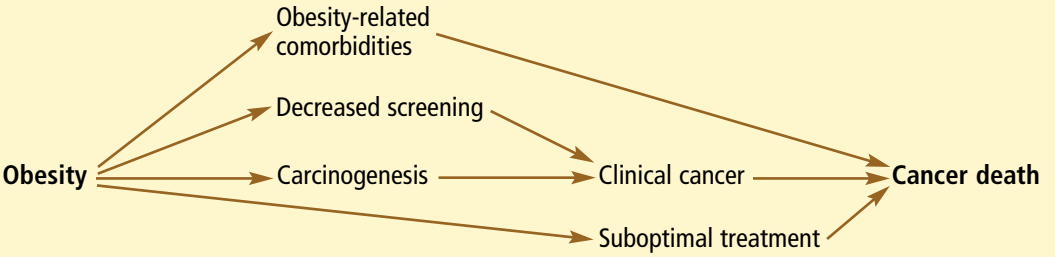

FIGURE 1

parities could not be explained by differences in the rate of physician recommendation for screening, suggesting that obese patients tend to be less interested or less able to undergo cancer screening. In a later study,[27] Wee et al found that some obese white women delayed cervical cancer screening because they found it painful, uncomfortable, or embarrassing.

Many obese patients have chronic medical conditions such as diabetes, hypertension, hyperlipidemia, and osteoarthritis that require a substantial amount of the health care provider's time to adequately manage, possibly leaving less time to address cancer screening in a regular office visit. Lipscombe et al[28] found a lower mammography rate among women with diabetes and attributed it to the complexity of managing diabetes. Lubitz et al[29] found that obese women were more likely to put off Pap testing because of acute illness, vaginitis, and menstruation.

Obesity-related comorbidities compete with screening for the provider's time

Since many providers do not have an effective reminder system to prompt them to provide appropriate cancer screening, more pressing medical concerns may take priority during appointments. Steps can be taken to improve this situation (see below).

Screening may be less effective in obese patients

Obesity may pose certain technical challenges in screening for cancer.

Clinical breast examinations may be less reliable because increased tissue volume may make some tumors difficult to palpate. Stilll, mammography seems to be equally effective in detecting breast cancer in obese and nonobese women.[26]

Pelvic examinations and Pap smears are often more difficult to perform in obese women. Many severely obese women need special accommodations such as larger examination tables, but even with these in place, it may be difficult to examine all the reproductive organs satisfactorily.

Similarly, prostate cancer screening is often of limited value because of the difficulty of performing a digital rectal examination in severely obese men. Furthermore, prostate-specific antigen levels tend to be lower in overweight and obese men with cancer, possibly because of lower circulating androgen levels.[30,31]

Socioeconomic issues (particularly inadequate insurance coverage) may pose a barrier to cancer screening. Obesity is more common in poorer people,[32,33] who are also more likely to be uninsured. Woolhandler and Himmelstein[34] found that uninsured women were less likely to undergo cervical and breast cancer screening.

Cancer is harder to treat in obese patients

Surgical procedures (eg, radical prostatectomy and rectal surgery) are technically more challenging in obese patients, who are more likely to have local cancer recurrence.[35–37] Obese people are more prone to blood loss requiring transfusions, have poorer wound healing, and have more pulmonary complications, but evidence for a higher rate of mortality from these complications is lacking.[38] Diabetes is associated with poorer cancer outcomes.[39]

Cancer treatment is also more difficult in obese patients because of uncertainty and lack of consensus about appropriate dosing of chemotherapy and radiation. An international survey of bone marrow transplant centers

found that some centers calculate dosage on the basis of body surface area, others use ideal body weight, and others use a variation of these methods.[40] Underdosing of chemotherapy for breast cancer among obese women has been reported[41–43] and may be associated with poorer outcomes. Nevertheless, data on the appropriate dosing of chemotherapeutic agents in obese patients are limited, and the effects that this potential underdosing might have on mortality rates are unclear.[44] Radiation treatment is as effective in obese as in nonobese cancer patients, but the appropriate dose and field may be more difficult to determine for obese patients.[45]

RECOMMENDATION: SET UP SCREENING PROTOCOLS

Physicians should seek to aggressively identify and treat cancers at an early stage in their obese patients. Given the competing medical problems often encountered in these patients, it may be challenging for physicians and patients to set priorities for cancer screening. A review of physician reminder systems for gynecologic cancer screening has demonstrated that both paper and electronic reminder systems are helpful.[46]

Another approach to increasing cancer screening rates involves aligning physicians' financial incentives toward particular outcome measurements, often referred to as "pay for performance": one group with such a system had increased cervical cancer screening rates.[47]

Physicians should devise ways to systematically screen all their patients for malignancy—regardless of comorbid conditions—and to educate their obese patients on the higher risk of malignancy and malignancy-related mortality that they face.

REFERENCES

1. **Hedley AA, Ogden CL, Johnson CL, Carroll MD, Curtin LR, Flegal KM.** Prevalence of overweight and obesity among US children, adolescents, and adults, 1999–2002. JAMA 2004; 291:2847–2850.
2. **Stein CJ, Colditz GA.** The epidemic of obesity. J Clin Endocrinol Metab 2004; 89:2522–2525.
3. **Flegal KM, Graubard BI, Williamson DF, Gail MH.** Excess deaths associated with underweight, overweight, and obesity. JAMA 2005; 293:1861–1867.
4. **Mokdad AH, Marks JS, Stroup DF, Gerberding JL.** Correction: actual causes of death in the United States, 2000. JAMA 2005; 293:293–294.
5. **Ford ES, Giles WH, Dietz WH.** Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA 2002; 287:356–359.
6. **Whitlock G, Lewington S, Mhurchu CN.** Coronary heart disease and body mass index: a systematic review of the evidence from larger prospective cohort studies. Semin Vasc Med 2002; 2:369–381.
7. **Wang TJ, Parise H, Levy D, et al.** Obesity and the risk of new-onset atrial fibrillation. JAMA 2004; 292:2471–2477.
8. **Visscher TL, Seidell JC.** The public health impact of obesity. Annu Rev Public Health 2001; 22:355–375.
9. **Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH.** The disease burden associated with overweight and obesity. JAMA 1999; 282:1523–1529.
10. **Lee ES, Kim YH, Beck S, Lee S, Oh SW.** Depressive mood and abdominal fat distribution in overweight premenopausal women. Obes Res 2005; 13:320–325.
11. **Osler M.** Obesity and cancer. A review of epidemiological studies on the relationship of obesity to cancer of the colon, rectum, prostate, breast, ovaries, and endometrium. Dan Med Bull 1987; 34:267–274.
12. **Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ.** Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003; 348:1625–1638.
13. **Calle EE, Kaaks R.** Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer 2004; 4:579–591.
14. **World Health Organization.** IARC/WHO handbook of cancer prevention. 1st ed. Lyon: IARC Press; 2002. Weight control and physical activity; vol 6.
15. **Jee SH, Kim HJ, Lee J.** Obesity, insulin resistance and cancer risk. Yonsei Med J 2005; 46:449–455.
16. **Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM.** Fasting serum glucose level and cancer risk in Korean men and women. JAMA 2005; 293:194–202.
17. **Khandwala HM, McCutcheon IE, Flyvbjerg A, Friend KE.** The effects of insulin-like growth factors on tumorigenesis and neoplastic growth. Endocr Rev 2000; 21:215–244.
18. **Frystyk J, Vestbo E, Skjaerbaek C, Mogensen CE, Orskov H.** Free insulin-like growth factors in human obesity. Metabolism 1995; 44(suppl 4):37–44.
19. **Nam SY, Lee EJ, Kim KR, et al.** Effect of obesity on total and free insulin-like growth factor (IGF)-1, and their relationship to IGF-binding protein (BP)-1, IGFBP-2, IGFBP-3, insulin, and growth hormone. Int J Obes Relat Metab Disord 1997; 21:355–359.
20. **Jenkins PJ.** Acromegaly and cancer. Horm Res 2004; 62(suppl 1):108–115.
21. **Dandona P, Aljada A, Chaudhuri A, Mohanty P, Garg R.** Metabolic syndrome: a comprehensive perspective based on interactions between obesity, diabetes, and inflammation. Circulation 2005; 111:1448–1454.
22. **Key TJ, Appleby PN, Reeves GK, et al; Endogenous Hormones Breast Cancer Group.** Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. J Natl Cancer Inst 2003; 95:1218–1226.
23. **Antunes CM, Strolley PD, Rosenshein NB, et al.** Endometrial cancer and estrogen use. Report of a large case-control study. N Engl J Med 1979; 300:9–13.
24. **Rossouw JE, Anderson GL, Prentice RL, et al; Writing Group for the Women's Health Initiative Investigators.** Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002; 288:321–333.
25. **Rosen AB, Schneider EC.** Colorectal cancer screening disparities related to obesity and gender. J Gen Intern Med 2004; 19:332–338.
26. **Wee CC, McCarthy EP, Davis RB, Phillips RS.** Screening for cervical and breast cancer: is obesity an unrecognized barrier to preventive care? Ann Intern Med 2000; 132:697–704.
27. **Wee CC, Phillips RS, McCarthy EP.** BMI and cervical cancer screening among white, African-American, and Hispanic women in the United States. Obes Res 2005; 13:1275–1280.
28. **Lipscombe LL, Hux JE, Booth GL.** Reduced screening mammography among women with diabetes. Arch Intern Med 2005; 165:2090–2095.

29. **Lubitz RM, Litzelman DK, Dittus RS, Tierney WM.** Is obesity a barrier to physician screening for cervical cancer? Am J Med 1995; 98:491–496.
30. **Hammarsten J, Hogstedt B.** Clinical, haemodynamic, anthropometric, metabolic and insulin profile of men with high-stage and high-grade clinical prostate cancer. Blood Press 2004; 13:47–55.
31. **Baillargeon J, Pollock BH, Kristal AR, et al.** The association of body mass index and prostate-specific antigen in a population-based study. Cancer 2005; 103:1092–1095.
32. **Ford ES, Mokdad AH, Giles WH.** Trends in waist circumference among U.S. adults. Obes Res 2003; 11:1223–1231.
33. **Drewnowski A, Specter SE.** Poverty and obesity: the role of energy density and energy costs. Am J Clin Nutr 2004; 79:6–16.
34. **Woolhandler S, Himmelstein DU.** Reverse targeting of preventive care due to lack of health insurance. JAMA 1988; 259:2872–2874.
35. **Freedland SJ, Grubb KA, Yiu SK, et al.** Obesity and capsular incision at the time of open retropubic radical prostatectomy. J Urol 2005; 174:1798–1801.
36. **Freedland SJ, Aronson WJ, Kane CJ, et al.** Impact of obesity on biochemical control after radical prostatectomy for clinically localized prostate cancer: a report by the Shared Equal Access Regional Cancer Hospital database study group. J Clin Oncol 2004; 22:446–453.
37. **Meyerhardt JA, Tepper JE, Niedzwiecki D, et al.** Impact of body mass index on outcomes and treatment-related toxicity in patients with stage II and III rectal cancer: findings from Intergroup Trial 0114. J Clin Oncol 2004; 22:648–657.
38. **Modesitt SC, van Nagell JR Jr.** The impact of obesity on the incidence and treatment of gynecologic cancers: a review. Obstet Gynecol Surv 2005; 60:683–692.
39. **Richardson LC, Pollack LA.** Therapy insight: influence of type 2 diabetes on the development, treatment and outcomes of cancer. Nat Clin Pract Oncol 2005; 2:48–53.
40. **Grigg A, Harun MH, Szer J.** Variability in determination of body weight used for dosing busulphan and cyclophosphamide in adult patients: results of an international survey. Leuk Lymphoma 1997; 25:487–491.
41. **Colleoni M, Li S, Gelber RD, et al; International Breast Cancer Study Group.** Relation between chemotherapy dose, oestrogen receptor expression, and body-mass index. Lancet 2005; 366:1108–1110.
42. **Griggs JJ, Sorbero ME, Lyman GH.** Undertreatment of obese women receiving breast cancer chemotherapy. Arch Intern Med 2005; 165:1267–1273.
43. **Berclaz G, Li S, Price KN, et al; International Breast Cancer Study Group.** Body mass index as a prognostic feature in operable breast cancer: the International Breast Cancer Study Group experience. Ann Oncol 2004; 15:875–884.
44. **Bastarrachea J, Hortobagyi GN, Smith TL, Kau SW, Buzdar AU.** Obesity as an adverse prognostic factor for patients receiving adjuvant chemotherapy for breast cancer. Ann Intern Med 1994; 120:18–25.
45. **Luchka K, Shalev S.** Pelvic irradiation of the obese patient: a treatment strategy involving megavoltage simulation and intratreatment setup corrections. Med Phys 1996; 23:1897–1902.
46. **Kupets R, Covens A.** Strategies for the implementation of cervical and breast cancer screening of women by primary care physicians. Gynecol Oncol 2001; 83:186–197.
47. **Rosenthal MB, Frank RG, Li Z, Epstein AM.** Early experience with pay-for-performance: from concept to practice. JAMA 2005; 294:1788–1793.

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