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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/m² 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/m²).

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/m²) or obese (BMI ≥ 30 kg/m²).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/M ²)	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.

ADAPTED WITH PERMISSION FROM CALLE EE, RODRIGUEZ C, WALKER-THURMOND K, THUN MJ. OVERWEIGHT, OBESITY, AND MORTALITY FROM CANCER IN A PROSPECTIVELY STUDIED COHORT OF US ADULTS. *N ENGL J MED* 2003; 348:1625–1638. COPYRIGHT © 2003 MASSACHUSETTS MEDICAL SOCIETY. ALL RIGHTS RESERVED.

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 al¹² 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 Schneider²⁵ 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

TABLE 2

Cancer Prevention Study II: Cancer mortality risk in obese women

CANCER TYPE	BMI (KG/M ²)	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.

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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-

Possible mechanisms for the relationship between obesity and cancer death

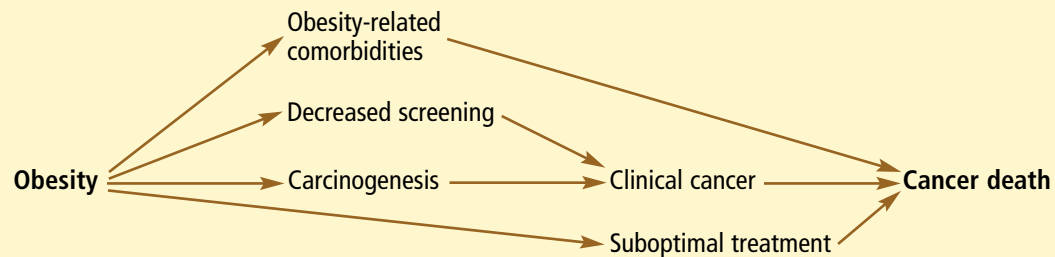


FIGURE 1

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 al²⁸ found a lower mammography rate among women with diabetes and attributed it to the complexity of managing diabetes. Lubitz et al²⁹ found that obese women were more likely to put off Pap testing because of acute illness, vaginitis, and menstruation.

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. Still, 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 Himmelstein³⁴ 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

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



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.

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