Report

Body mass index and survival after cancer diagnosis: A pan-cancer cohort study of 114 430 patients with cancer

Huakang Tu,[1,2,3] Jennifer L. McQuade,[4] Michael A. Davies,[4] Maosheng Huang,[2] Kunlin Xie,[2,5] Yuanqing Ye,[2] Wong-Ho Chow,[2] Alma Rodriguez,[6] and Xifeng Wu[1,2,3,7,*]

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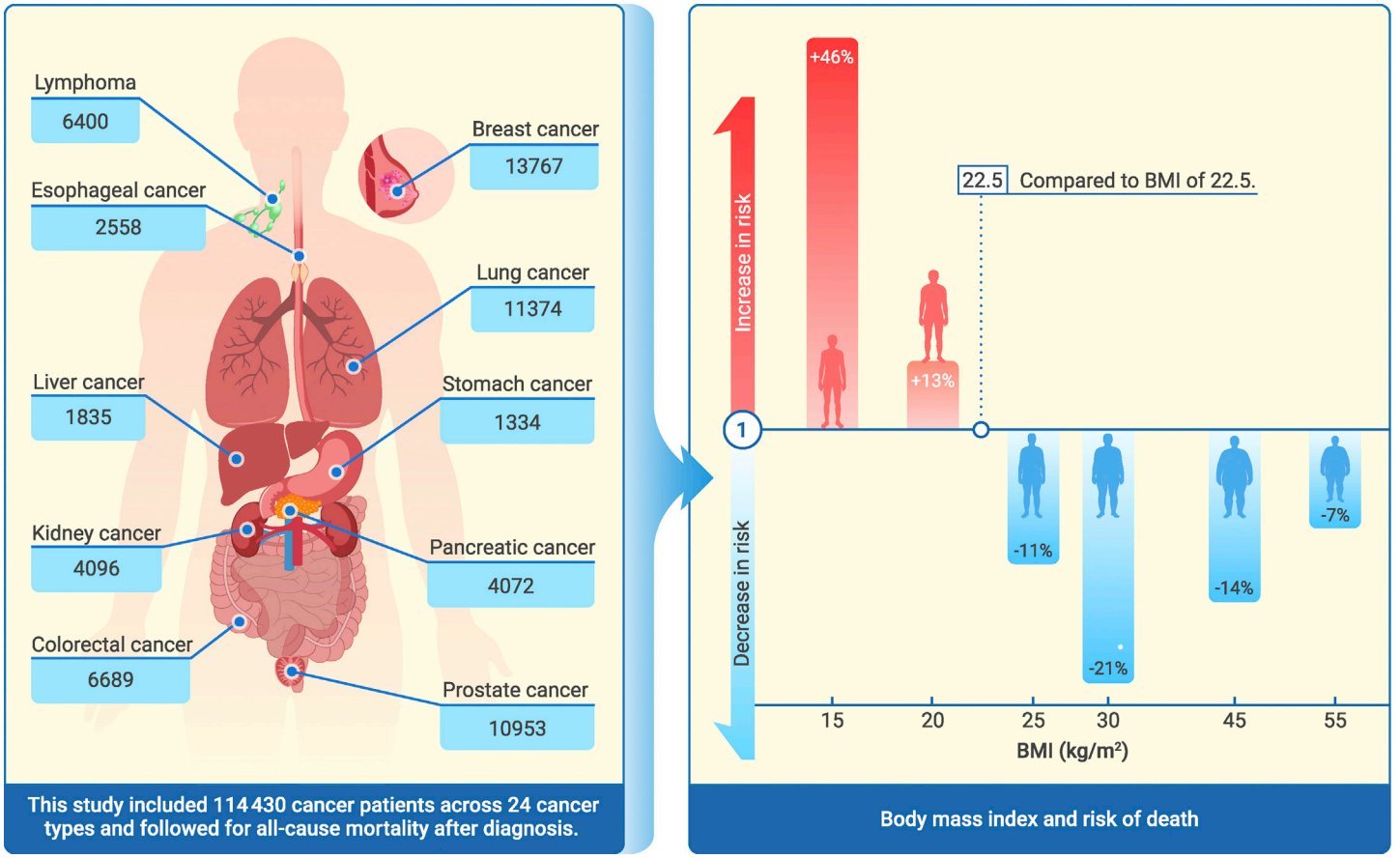
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Excess body weight increases the risk of developing cancer in general population
- Overweight or mild obesity was associated with better survival in cancer patients
- It may be harmful for overweight or mildly obese cancer patients to lose weight

Report

Body mass index and survival after cancer diagnosis: A pan-cancer cohort study of 114 430 patients with cancer

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The recommendation encouraging patients with cancer to keep a normal body mass index (BMI) is largely extrapolated from data on risk of developing cancer. We tested the prospective association between peri-diagnostic (within 1 year post-diagnosis) BMI and all-cause mortality in patients with incident cancers. During 7.2 years of follow-up, 42% (48,340) of the 114 430 patients with cancer died. Spline analysis revealed that compared with a BMI of 22.5, a BMI lower than 22.5 was associated with increased risk of all-cause mortality across 24 cancer types. A BMI higher than 22.5 was associated with reduced all-cause mortality, while a non-linear association was observed; the lowest risk was found at a BMI of 29.6–34.2, and the risk started to return to and above unity at very high BMI values. The reduced mortality risk of high BMI was observed in 23 of 24 cancer types and maintained after attempts to remove potential selection bias, confounding by smoking and comorbidities, and reserve causality. Compared with a normal BMI of 18.5–24.9, the hazard ratios were 0.85 (95% confidence interval [CI], 0.83–0.87) for an overweight BMI (25–29.9) and 0.82 (0.80–0.85) for an obese BMI (≥30), and the associations were generally consistent across cancer types and various subgroups. Obese BMI was associated with increased life expectancy, up to 6 years among men and 3 years among women. In conclusion, while overweight/obese BMI increases the risk of developing cancer in the general population, overweight/obese peri-diagnostic BMI was associated with longer survival in cancer patients.

INTRODUCTION

It is well established that excess body weight increases risk of overall mortality and risk of developing many different malignancies in the general population.[1,2] In contrast, paradoxical associations were found in populations with a chronic disease (including cardiovascular disease, pulmonary disease, and end-stage renal disease) where an overweight or obese body mass index (BMI) appears associated with lower mortality risk, a phenomenon called the "obesity paradox."[3]

Patients with cancer and cancer survivors, a large and growing population, are greatly interested in seeking information on modifying lifestyle factors to improve prognosis.[4] Current guidelines recommend patients with cancer and cancer survivors to achieve or maintain a normal body weight,[5–7] and those recommendations are largely extrapolated from prevention data. However, the biology of excess body weight in cancer development may differ from that in cancer prognosis. To date, the effects of body weight after diagnosis on cancer outcomes are not fully understood, and no evidence from a randomized trial to examine the impact of intentional weight change on cancer outcomes is available.[8]

There is conflicting data on the association of body weight with outcomes among patients with cancer. While some studies suggest that an overweight/obese BMI may predict favorable outcomes in patients with cancer,[9–18] supporting the obesity paradox in cancer,[15,19] other studies suggest the opposite.[20–23] There is some evidence that associations may vary by cancer site, stage, and treatment.[13,14,24] Inconsistent results in previous studies may also arise from methodological issues such as relatively small sample size, single measurement of BMI, timing of BMI measurement (ie, pre-diagnostic/early life, peri-diagnostic, or before certain cancer therapy), body weight and height that were self-reported, granularity of BMI cutoffs selected, poor statistical methodology (ie, treating BMI as categorized or linear), selection bias, confounding by unmeasured variables (especially smoking and comorbidities), and reverse causality.[15,19,25–28] Moreover, most studies to date have been conducted in common cancers, and data on relatively uncommon cancers are sparse.

To address these potential limitations, we systematically studied a large prospective cohort of 114 430 adult patients with cancer to investigate the association of peri-diagnostic (within 1 year after diagnosis[15,29]) BMI with all-cause mortality across 24 cancer types.

METHODS

Study population

Study participants were accrued from the MD Anderson Cancer Patients and Survivors Cohort, which was previously described in detail.[30] The inclusion criteria for the current analysis were 1) newly diagnosed (registered at MD Anderson within 1 year of diagnosis) and histologically confirmed cancer; 2) age ≥18 years at the time of diagnosis; 3) at least one BMI measurement obtained within 1 year after diagnosis; 4) core epidemiological data available from the patient history database (PHDB). The final study cohort consisted of 114 430 patients with cancer diagnosed between 2001 and 2014. This study was approved by The University of Texas MD Anderson Cancer Center institutional review board, and informed consent was obtained through protocol Lab03-0320 to authorize data processing and analysis.

Data collection

Healthcare professionals measured weight and height at medical visits as standard of care assessments, which were used to derive BMI (weight [kg]/height [m]^2) at each visit. The median number of weight and BMI measurements per patient was 12 (range 1–1076). The standardized PHDB questionnaire, a mandatory component of each patient's primary medical evaluation, collects comprehensive baseline information at first visit to MD Anderson such as demographics, tobacco and alcohol use history, medical history, current comorbid conditions, and quality of life (based on the Short Form-12 v.1[31]). Patients with more advanced/aggressive cancer often lose weight and may migrate to a lower BMI; therefore, information on prior weight loss is important for assessing potential bias due to reverse causality. Information regarding prior weight loss was available in a random subset of 24 962 patients through manual abstraction from the question on prior weight loss in the PHDB questionnaire (this information was not entered into the database initially). To assess whether the associations among the subset could represent those among the overall cohort, we compared the distribution of patient characteristics in this subset with that in the overall cohort. The distribution of patient characteristics in this subset was comparable to that in the overall cohort. The clinical coding specialists at the institutional tumor registry abstracted clinical data on tumor site, stage, histology, grade, prior treatment, and treatment at MD Anderson.

Ascertainment of mortality

Follow-up procedures were previously reported.[30] Briefly, the vital status of all patients is ascertained annually via active and passive approaches by the institutional tumor registry. Matching with appointment files at MD Anderson separates patients with a recent medical visit from those without one in the previous 12–15 months. The vital status of the latter group is then inquired by follow-up letters and by telephone calls to patients who have not

Table 1. Patient characteristics by weight status according to BMI (kg/m^2)

Characteristics (N = 114 430)[a]	Underweight (n = 2268)	Normal weight (n = 36 060)	Overweight (n = 41 017)	Obese (n = 35 085)
Mean (SD) BMI (kg/m^2)	17.3 (1.2)	22.5 (1.7)	27.4 (1.4)	35.2 (5.7)
Mean (SD) age at diagnosis, years	55.6 (16.3)	56.5 (15.3)	58.4 (13.5)	56.8 (12.9)
Gender				
Male	692 (30.5)	15 396 (42.7)	25 177 (61.4)	18 906 (53.9)
Female	1576 (69.5)	20 664 (57.3)	15 840 (38.6)	16 179 (46.1)
Race/ethnicity[b]				
White	1628 (71.8)	28 476 (79.0)	32 431 (79.1)	26 498 (75.5)
Black	266 (11.7)	2150 (6)	2773 (6.8)	3592 (10.2)
Other	374 (16.5)	5434 (15)	5813 (14.1)	4995 (14.3)
Marital status[c]				
Married	1348 (59.8)	25 488 (71)	31 167 (76.3)	25 657 (73.4)
Single	428 (19.0)	4729 (13.2)	4016 (9.8)	4022 (11.5)
Other	480 (21.3)	5705 (15.9)	5687 (13.9)	5259 (15.1)
Education[d]				
Some college/ associate degree or less	1258 (65.8)	17 329 (54.6)	20 739 (57)	20 014 (64.6)
Bachelor or higher	654 (34.2)	14 418 (45.4)	15 664 (43)	10 968 (35.4)
Ever smokers[e]	1289 (58.3)	17 758 (50.6)	20 670 (51.6)	16 588 (48.5)
Ever drinkers[f]	1143 (52.7)	20 190 (58.1)	23 484 (59.3)	16 996 (50.2)
Poor health[g]	306 (17.2)	2312 (7.8)	1791 (5.2)	1689 (5.8)
Number of comorbid conditions[h]				
0	935 (41.9)	14 362 (40.7)	13 430 (33.5)	8281 (24.3)
1–3	1195 (53.5)	19 326 (54.8)	24 241 (60.5)	22 515 (66)
≥4	104 (4.7)	1600 (4.5)	2396 (6.0)	3302 (9.7)
Tumor stage[i]				
Carcinoma *in situ*	20 (1.1)	868 (2.9)	820 (2.4)	802 (2.7)
Post-treatment NED	176 (9.3)	4082 (13.5)	4504 (12.9)	4435 (14.9)
Other	1691 (89.6)	25 387 (83.7)	29 460 (84.7)	24 535 (82.4)
Prior treatment				
Surgery	612 (27)	10 421 (28.9)	11 305 (27.6)	10 373 (29.6)
Radiation therapy	253 (11.2)	2364 (6.6)	2159 (5.3)	1646 (4.7)
Chemotherapy	484 (21.3)	5552 (15.4)	5330 (13)	4033 (11.5)
Endocrine therapy	57 (2.5)	1010 (2.8)	1561 (3.8)	1428 (4.1)
Immunotherapy	74 (3.3)	807 (2.2)	922 (2.2)	729 (2.1)
Treatment at MD Anderson				
Surgery	512 (22.6)	10 987 (30.5)	13 743 (33.5)	12 509 (35.7)
Radiation therapy	510 (22.5)	6405 (17.8)	6845 (16.7)	5460 (15.6)
Chemotherapy	812 (35.8)	12 184 (33.8)	12 557 (30.6)	9943 (28.3)
Endocrine therapy	75 (3.3)	1794 (5)	2499 (6.1)	2346 (6.7)
Immunotherapy	93 (4.1)	1820 (5)	2095 (5.1)	1738 (5)

BMI was grouped according to standard WHO criteria (underweight <18.5; normal 18.5–24.9; overweight 25–29.9; obese ≥30). NED, no evidence of disease.
[a]Values are numbers (percentages) unless stated otherwise.
[b]Self-reported.
[c]Missing for 444 patients.
[d]Missing for 13 386 patients.
[e]Missing for 2889 patients.
[f]Missing for 3986 patients.
[g]Missing for 19 842 patients.
[h]Missing for 2743 patients and conditions including heart disease, high blood pressure, circulation disease, stroke, seizure, lung disease, liver disease, kidney/urinary disease, bleeding disorder, psychological/psychiatric disease, diabetes or sugar in urine, thyroid disease, frequent infections, and HIV/AIDS.
[i]Missing for 17 650 patients. Given the large available sample size, all differences in baseline characteristics between weight classifications are statistically significant ($p < 0.01$), with one exception being receipt of immunotherapy treatment.

responded to letters. For patients who are not reached by these active approaches (estimated to be <5%), the vital status is further ascertained by passive matching to the Social Security Death Index and State Bureau of Vital Statistics. The last date of available follow up was February 16, 2018.

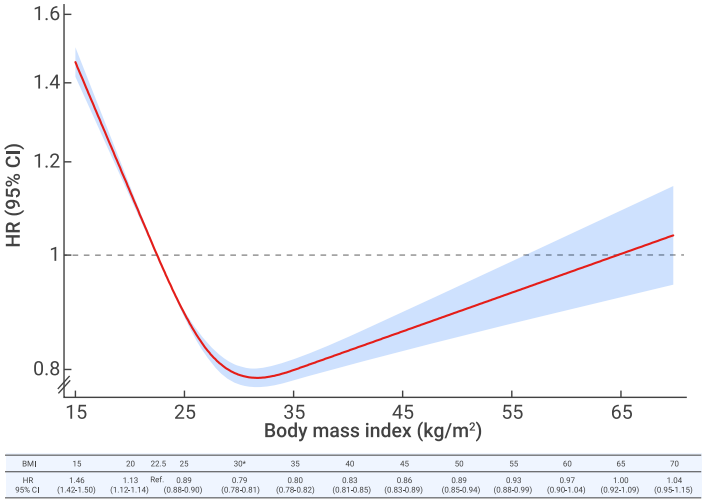
Statistical analysis

STATA statistical software and Statistics Analysis System (SAS) were used to perform all statistical analyses. The time to event was accumulated from the time at cancer diagnosis to the time at death or last contact, whichever came first. We calculated mean peri-diagnostic (within 1 year after diagnosis[15,29]) BMI based on all the post-diagnosis BMI measurements in this time frame weighted proportionally to the time elapsed between measurements.[32] Overall and within each of the 24 cancer types, we used restricted cubic spline analysis to assess the multivariable-adjusted association between BMI as a continuous variable and all-cause mortality. Potential confounders to consider were selected according to *a priori* knowledge, and the final model included potential confounders that were in association with both BMI and all-cause mortality and were not in the causal pathway. The number of knots in spline analysis was chosen to be three. A BMI of 22.5 was chosen as the reference as it is the mid-point of the BMI category 20 to 25, which was associated with the lowest all-cause mortality in large prospective studies in the general population. Also, a BMI of 22.5 would provide a more stable reference compared with extreme BMI values. As a sensitivity analysis to assess potential bias due to prior weight loss, we conducted a stratified analysis among patients with or without weight loss prior in the subset with weight-loss information. Then, BMI was grouped according to standard WHO criteria (underweight <18.5; normal 18.5–24.9; overweight 25–29.9; obese ≥30). The risk of death across four BMI groups was plotted and estimated using the Kaplan–Meier function. We used the Cox proportional hazards model with time on study as the timescale to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) after adjustment of potential confounders including age at diagnosis (continuous); sex (male, female); race/ethnicity (white, black, Hispanic, Asian/Pacific islander, other); marital status (married, single, other); education (high school or less, some college/associate degree, bachelor or higher); smoking status (current, former, never); alcohol consumption (current, former, never); self-rated overall health status (excellent, very good, good, fair, poor); number of comorbidities (0, 1, 2, 3, ≥4); tumor stage (carcinoma *in situ*, localized, regional, distant, post-treatment no evidence of disease); prior treatment (surgery, radiation therapy, chemotherapy, endocrine therapy, immunotherapy); treatment at MD Anderson (surgery, radiation therapy, chemotherapy, endocrine therapy, immunotherapy); and specific cancer types. The proportionality of the Cox proportional hazards model was examined by visual inspection of the log–log survival plots. We performed multiple imputation with 10 iterations for missing data, and analyses were performed on the dataset with imputed data using the mi estimate command in STATA. However, the results without imputation were similar. Life expectancy was estimated by the Chiang's method of abridged life table having 85+ open ends with 5-year age interval.[33]

RESULTS

Patient baseline characteristics

The distribution of BMI in the study population is presented in Table S1. The selected patient characteristics at first visit to MD Anderson by peri-diagnostic weight status are presented in Table 1. Among the 114 430 patients with cancer



BMI	15	20	22.5	25	30*	35	40	45	50	55	60	65	70
HR	1.46	1.13	Ref.	0.89	0.79	0.80	0.83	0.86	0.89	0.93	0.97	1.00	1.04
95% CI	(1.42-1.50)	(1.12-1.14)		(0.88-0.90)	(0.78-0.81)	(0.78-0.82)	(0.81-0.85)	(0.83-0.89)	(0.85-0.94)	(0.88-0.99)	(0.90-1.04)	(0.92-1.09)	(0.95-1.15)

Figure 1. Association of peri-diagnostic body mass index (BMI) with all-cause mortality in spline analysis Note: BMI of 22.5 kg/m^2 was the reference value. Solid lines represent hazard ratios (HRs), and dashed lines are 95% confidence intervals (95% CIs) calculated in restricted cubic spline Cox proportional hazards regression adjusted for age, sex, race/ethnicity, marital status, education, smoking status, alcohol consumption, self-rated overall health status, number of comorbidities, tumor stage, prior treatment, treatment at MD Anderson, and specific cancer types

enrolled, 30.7% were obese, 35.8% were overweight, 31.5% were normal weight, and 2% were underweight. The percentage of patients with cancer with distant disease was 28.7% (regional disease: 20.4%; localized disease: 21.7%; carcinoma *in situ*: 2.2%; post-treatment with no evidence of disease: 11.5%; unstaged: 15.4%). Patients who were obese or overweight were more likely to be of increased age, male sex, Hispanic/black race and ethnicity, married marital status, lower education, comorbid conditions, and earlier tumor stages.

BMI and all-cause mortality overall and across cancer sites and subgroups

During follow up (median of 7.2 years), 529 712 person years were accumulated, and 48 340 deaths were recorded. Spline analysis revealed a J-shaped association of peri-diagnostic BMI with risk of death (Figure 1) in the pooled population across cancer types. Specifically, compared with a BMI of 22.5, a BMI lower than 22.5 was associated with increased risk of all-cause mortality. A BMI higher than 22.5 was associated with reduced all-cause mortality, while a non-linear association was observed; the lowest risk was found at a BMI of 29.6–34.2, and the risk started to return to and above unity at very high BMI values. The associations were similar when using the first available BMI within 1 year or 90 days after diagnosis.

Figure 2 shows the results from spline analysis for each type of cancer. For most cancer types (15 out of 24), the shape of the association was similar to the overall association from the pooled analysis across cancer types, and the lowest mortality risk was generally observed for a BMI between 30 and 35. For lung cancer, colorectal cancer, non-melanoma skin cancer, and thyroid cancer, the risk plateaued for a BMI over 30. For pancreatic cancer, endocrine related cancer, ovary cancer, and uterine cancer, BMI was inversely associated with the risk of death. For central nervous system cancer, BMI was positively associated with risk of death. As shown in Figure 3, the association between BMI and risk of death was generally consistent within (disease-combined) subgroups defined by tumor stage (Figure 3A) and other variables of prognostic significance including weight loss prior to the first visit at MD Anderson (Figure 3B), sex (Figure 3C), age at diagnosis (Figure S2), race/ethnicity (Figure S3), smoking status (Figure S4), number of comorbid conditions (Figure S5), tumor differentiation (Figure S6), and treatment regimen (Figure S7). Also, generally consistent trends were observed for obesity-related cancers (defined according to the IARC Working Group[2]) and non–obesity-related cancers (Figure S8), after sequentially deleting person years within 1 to 4 years in the pooled population across cancer types (Figure S9), after further adjustment of family history of cancers (Figure S10A), where the follow up started from the time of the last BMI measurement for each patient (Figure S10B), and among never smokers for non–obesity-related cancers and after excluding the first 2 years of follow up (Figure S11).

Weight status and risk of death overall and across cancer sites and subgroups

Kaplan–Meier survival curves in the pooled population across cancer types (Figure S12) showed that higher BMI groups were associated with better overall survival. Compared with patients of normal weight, patients who were overweight and obese had a 15% (HR = 0.85, 95% CI = 0.83–0.87) and 18% (HR = 0.82, 95% CI = 0.80–0.85) reduced risk of death, respectively, and patients who were underweight had a 44% increased risk of death (HR = 1.44, 95% CI = 1.36–1.53).

Weight status and life expectancy

Overweight and obese BMIs were associated with longer life expectancy (Figure 4), whereas an underweight BMI was associated with shorter life expectancy. Among men, patients who were overweight and obese had up to 4.5- and 5.9-year-longer life expectancies (at diagnosis age of 40), respectively, than patients of normal weight. Likewise, female patients who were overweight and obese had up to 2.4- (at diagnosis age of 45–55) and 3-year-longer (at diagnosis age of 50) life expectancies, respectively.

DISCUSSION

In contrast to the current clinical guidelines encouraging patients with cancer to achieve or maintain a normal BMI of 18.5–24.9 kg/m^2, spline analysis in our study showed that patients with a BMI of 29.6–34.2 had the lowest mortality risk. The reduced mortality risk of overweight or obese BMI was found in 23 of 24 specific cancers and was maintained after attempts to remove potential selection bias, confounding by smoking and comorbidities, and reserve causality. Patients with cancer who were overweight or obese had a 15% and 18% reduced risk of death, respectively.

Some posit that the observed paradoxical survival benefit among patients with cancer who were obese or overweight reflects a true biologic effect,[15,19,26,28,34,35] while others suspect that it is due to methodologic limitations such as a selection bias called collider bias, confounding by smoking and comorbidities, or reverse causality.[15,19,25–28] Before we interpret the clinical implications of our findings for patients with cancer, we must exhaustively exclude these potential methodologic limitations.

Collider bias might occur when associations between BMI and mortality in obesity-related cancers are studied because participants were selected into the analysis based on occurrence of obesity-related cancer (a collider) that is affected by BMI and shares risk factors with mortality.[36] Even though this bias is plausible for obesity-related cancers (eg, breast and colorectal), it has been shown that in order to reverse the causal effect, the collider bias has to be very strong.[37] By definition, collider bias should not be a methodological concern for non–obesity-related cancers. In the present study, to assess the potential impact of collider bias, we conducted stratified analysis by obesity-related cancers versus non–obesity-related cancers, and we found survival benefits of extra weight in obesity-related cancers as well as in non–obesity-related cancers. The second concern is confounding by smoking and comorbidities, which are associated with a lower BMI and poor survival in patients with cancer. In our study, the survival benefits of extra weight were observed regardless of smoking status, including in never smokers, and with additional adjustment of pack year of smoking (data not shown) and regardless of comorbidities. These findings suggest that collider bias and confounding by smoking and comorbidities cannot explain the survival benefits of overweight and obese BMIs in cancer.

A third concern is reverse causality.[15,19,25–28] Patients with more advanced/aggressive cancer often lose weight and may migrate to a lower BMI, so the cancers with poor prognosis might reversely cause lower BMI instead of the other way around. Several sensitivity analyses were conducted to address this. Though we did not have pre-diagnosis BMI on all patients, we did have data on prior weight loss for ~25,000 patients and found that associations were sustained among patients without prior weight loss. We further found that the reduced mortality risks of the patients who were overweight and obese were sustained in the subgroups with localized tumors or well-differentiated tumors, in those with good overall quality of life, and after sequentially removing patients who died early after cancer diagnosis. Thus, reverse causality cannot fully explain the survival benefits of overweight and obese BMIs in patients with cancer. However, it is worthwhile to point out that after attempts to remove potential selection bias and reserve causality, the associations were attenuated, but they did not disappear, suggesting that methodologic limitations indeed played a role but were not the

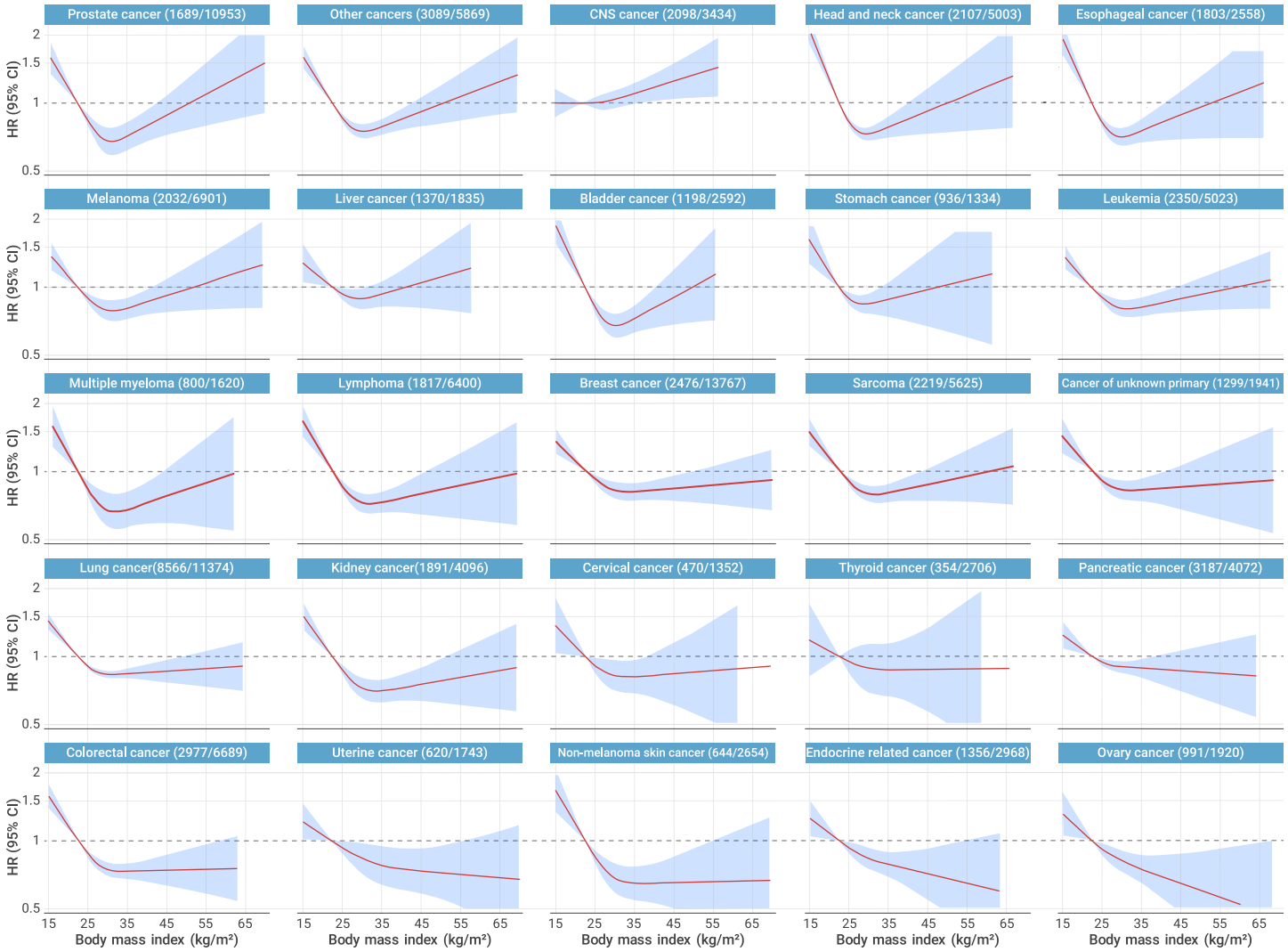


Figure 2. Association of peri-diagnostic BMI with risk of death in spline analysis by specific cancers Note: BMI of 22.5 kg/m^2 was the reference value. Solid lines represent HRs, and dashed lines are 95% CIs calculated in restricted cubic spline Cox proportional hazards regression adjusted for age, sex, race/ethnicity, marital status, education, smoking status, alcohol consumption, self-rated overall health status, number of comorbidities, tumor stage, prior treatment, and treatment at MD Anderson. Numbers under each cancer type represent the number of deaths/total number of patients for that cancer type

sole explanation for the survival benefits of overweight and obese BMI in patients with cancer.

It is biologically plausible that extra weight in patients with cancer may confer a survival advantage because extra weight serves as a physiologic and nutritional reserve to overcome the negative metabolic impact from tumor growth itself as well as treatments of cancers.[15,19,26,28,34,35] Patients with a high BMI generally have adequate lean body mass,[34,38,39] which is associated with better outcomes among patients with cancer.[19,34,38–40] Also, in the context of chronic illness, fat tissue (in particular, subcutaneous and gluteofemoral) has several beneficial effects (eg, secretion of cardioprotective adipokines such as adiponectin, protection against bone fracture) that may offset the adverse effects of overall adiposity.[28,41–45]

We found better overall survival in patients with cancer with an overweight or mildly obese BMI after diagnosis. Notably, we feel that our findings by no means stand against the need to curb the obesity epidemic worldwide, which increases the general population's burden from cancer and many other diseases.[2,46] However, it is biologically challenging to assume that the ideal body weight is the same for all individuals under all conditions.[47] Our findings are relevant only to patients with cancer among whom the ideal body weight may shift upward.[47] Furthermore, as the lowest mortality risk was found at a BMI of 29.6–34.2, our data do not support "the heavier the better." Finally, it should be noted that the current study only assessed BMI within 1 year after diagnosis, and the results should be interpreted within this peri-diagnosis setting; however, BMI may change throughout the cancer treatment and survivorship period along the course of the disease, and further studies are needed to examine the prognostic effect BMI during the recovery/survivorship phase.

Because of the obesity epidemic and the elevated cancer risk conferred by excess body weight, increasing numbers of patients with cancer are obese or overweight at diagnosis,[8] and evidence is limited to guide weight management in these patients. Current clinical guidelines recommend patients with cancer who are overweight or obese to lose weight.[5–7] The largest body of evidence supporting this recommendation is from early-stage breast cancer,[6,15] but the evidence was recently rated as "limited–suggestive" in the Continuous Update Project.[29] Without confirmatory evidence from randomized controlled trials showing that losing weight intentionally can improve cancer prognosis, it may not be warranted to recommend weight loss among patients with cancer with an overweight or mildly obese BMI in the post-diagnosis period. One randomized clinical trial in patients with prostate cancer showed that intentional weight loss may have adverse effects on the tumor.[48] Therefore, instead of focusing on weight loss, which may not improve cancer prognosis and even may even cause harms in patients with cancer, it might be more prudent to recommend other lifestyle modifications such as physical activity, healthy diet, and smoking cession. Results from this study warrant the exploration of potential mechanisms underlying the improved outcomes observed in patients with cancer who are obese and overweight.

Several strengths are noted in this study. First, we utilized a prospective pan-cancer cohort of 114 430 patients with cancer with comprehensive epidemiological and clinical data and long-term follow-up data. Second, a broad spectrum of

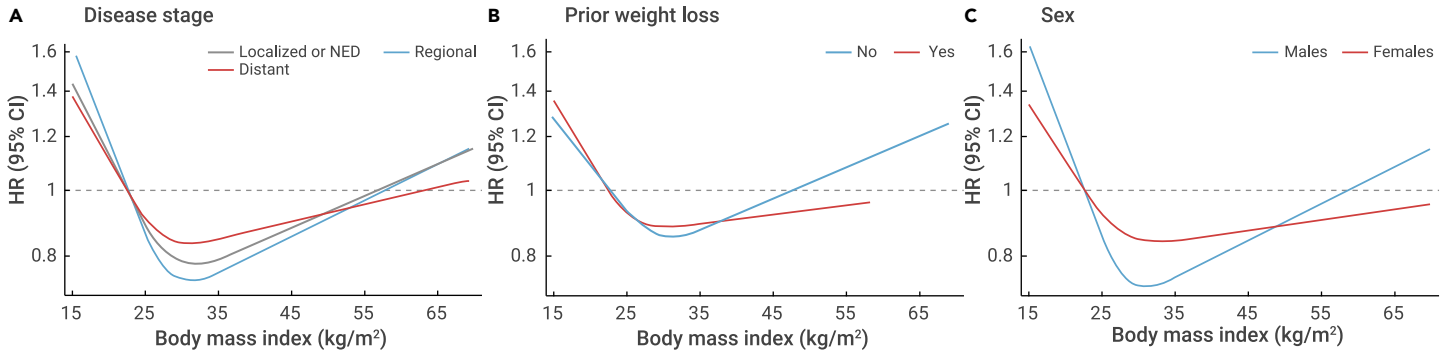


Figure 3. Association of peri-diagnostic BMI with risk of death in spline analysis Association of peri-diagnostic BMI with risk of death in spline analysis by disease stage **(A)**, prior weight loss **(B)**, and sex **(C)**. Note: BMI of 22.5 kg/m^2 was the reference value. Solid lines represent HRs calculated in restricted cubic spline Cox proportional hazards regression adjusted for age, sex, race/ethnicity, marital status, education, smoking status, alcohol consumption, self-rated overall health status, number of comorbidities, tumor stage, prior treatment, treatment at MD Anderson, and specific cancer types, wherever appropriate. p for interaction was <0.001, 0.54, and <0.001 for spline analysis by disease stage, prior weight loss, and sex, respectively. Information regarding prior weight loss was available through manual abstraction in a random subset of 24 962 patients (19 027 patients without prior weight loss and 5935 with prior weight loss)

24 specific cancers were simultaneously studied, with each cancer represented by at least 1000 cases. Third, we calculated the weighted mean BMI from multiple BMI measurements, which overcomes the limitation of using BMI at one time point. Fourth, trained staff measured weight and height, minimizing potential misclassification from self-reported weight and height.[49] Fifth, we conducted multiple sensitivity analyses to exclude potential artifact explanations raised in previous studies. Sixth, the patients in the cohort were diagnosed and treated within the last decade at one tertiary referral cancer hospital, hence treatment strategies were modern and standardized. Finally, because MD Anderson has a tumor registry department that comprehensively monitors patients with cancer over time, few individuals were lost to follow up.

We also acknowledge that our study has potential limitations. As in any observational study, we cannot confirm causality. However, the prospective design, strong association observed, results being consistent and biologically plausible, and comprehensive efforts to exclude methodological explanations lend support for causality. Second, even with comprehensive adjustment of potential confounding factors, we cannot exclude the possibility of residual confounding. For example, we did not collect information on passive smoking, treatment adherence, and dose. Also, we did not collect detailed behavioral data related to obesity and lifestyle, including diet, physical activity, and medication use. Third, we used BMI to define weight status, and data on other anthropometric indices such as waist circumference, waist–to–hip ratio, and body composition were not available. Unlike other indices and body composition, BMI is routinely and readily collected at medical visits, and it is the index currently used in guidelines to guide both patients with cancer and oncology providers on weight management.[5–7] Fourth, though consistent associations were observed across cancer sites, we cannot rule out that the association may vary by stage, treatment, molecular subtypes, or other factors for each specific cancer site.[14,23,24] Finally, we cannot infer the effects of an overweight or obese BMI on cancer-specific death or clinical outcomes at later time points not captured in this study.

In summary, though excessive body weight increases risk of developing cancer, our study shows that an overweight or mildly obese peri-diagnostic BMI is linked to improved survival among patients with cancer. These associations were maintained after attempts to remove non-causal explanations due to methodological limitations. These findings provide support for developing weight management strategy that is based on evidence in cancer care, and they suggest that the current universal recommendations for patients with cancer who are overweight or obese to lose weight should be revisited.[5–7]

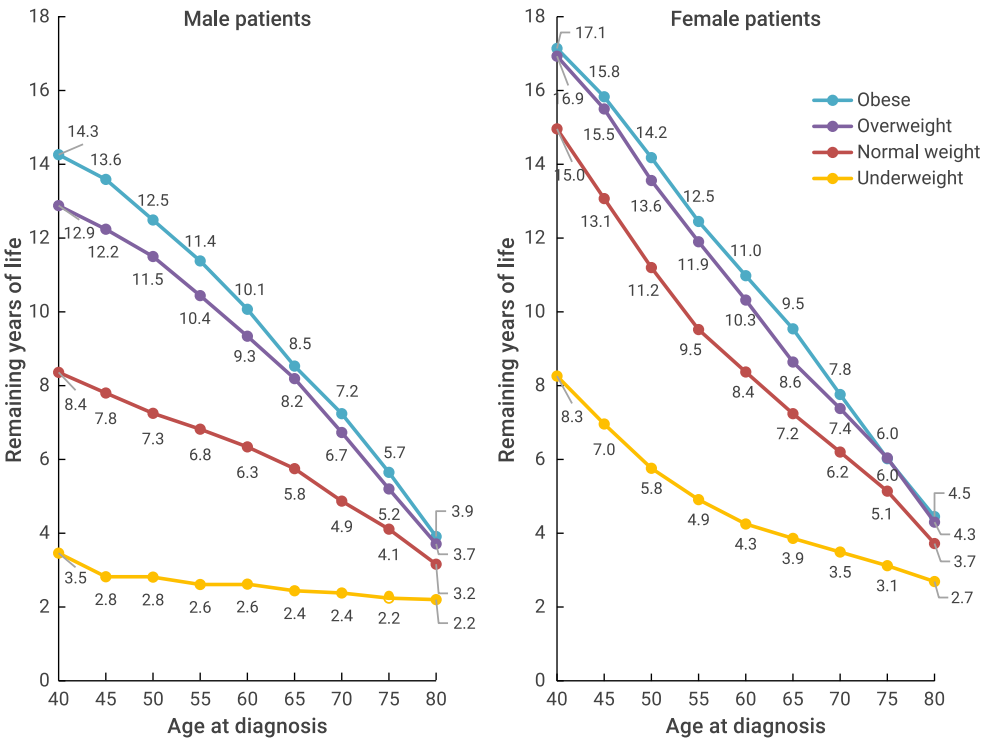


Figure 4. Life expectancy by peri-diagnostic weight status Life expectancy by peri-diagnostic weight status among male and female patients. Note: Underweight: BMI <18.5 kg/m^2; normal: BMI 18.5–24.9 kg/m^2; overweight: BMI 25–29.9 kg/m^2; obese: BMI ≥30 kg/m^2.

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AUTHOR CONTRIBUTIONS

X.W. and A.R. contributed to the collection, assembly, and quality control of the data; X.W. and H.T. were responsible for the conception and design of the study; H.T., Y.Y., M.H., and X.W. designed the strategies of data analysis and conducted the statistical analysis; X.W., H.T., J.L.M., M.A.D., K.X., Y.Y., W.-H.C., and A.R. interpreted the data. H.T. and X.W. drafted the report; All authors revised it critically for important intellectual content and agreed to submit the report for publication.

DECLARATION OF INTERESTS

The authors declare no competing interests.

SUPPLEMENTAL INFORMATION

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