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REVIEW ARTICLE

Obesity and Other Cancers

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ABSTRACT

Purpose
Evidence on overweight, obesity, and an increased risk of cancer continues to accumulate and was updated in the 2016 handbook on weight control from the International Agency for Research on Cancer (IARC). The underlying primary data, together with dose-response meta-analysis and, finally, pooled analysis of individual participant data, add insight into the relation between obesity and cancer risk and prognosis. We summarize the evidence for mortality from prostate cancer, hematologic malignancies, and kidney cancer.

Methods
We reviewed pooled analysis of rare end points across cohorts, regardless of primary results reported from the individual studies, further reducing risk of publication bias. Of these cancer sites, only kidney cancer was included in the IARC 2002 report, although mortality from prostate cancer and hematologic malignancies was noted in the American Cancer Society prospective cohort study in 2003. The 2016 update from the IARC added details for prostate and hematologic malignancies, classifying the evidence as sufficient to conclude that avoiding excess body fatness lowers the risk of multiple myeloma but found that the evidence for it lowering the risk of prostate cancer mortality or diffuse large B-cell lymphoma was limited.

Results
A higher body mass index is associated with an increased risk of advanced prostate cancer and prostate cancer mortality and is associated with worse survival in most subtypes of hematologic malignancies, in a dose-response fashion. Evidence for kidney cancer is built mostly on retrospective data, which supports an obesity paradox in patients with the clear cell variant; however, population-based cohort data indicate that a higher cohort-entry body mass index is associated with worse kidney cancer–specific survival.

Conclusion
Together, these data add support to the evidence for a growing cancer burden caused by adiposity in both early adult and later adult life, yet leave open the question of the means of weight management after diagnosis as a strategy to improve survival.

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INTRODUCTION

Here we review the current research addressing the role of adiposity/obesity in mortality and prognostic outcomes in prostate, hematologic, and renal cancers. Excess weight or adiposity is a common risk factor for cancer, progression, and nonsurvival; this provides a unique opportunity to address a modifiable risk factor through primary and secondary interventions. Evidence reviewed by the International Agency for Research on Cancer (IARC) and the World Cancer Research Fund support the finding that being overweight or obese is an established cause of several cancers including breast, endometrium, esophagus (adenocarcinoma), renal, and colon and rectum.[1] Since the IARC report in 2002, evidence has expanded to suggest an association between a higher body mass index (BMI) and advanced prostate or prostate cancer mortality and several hematologic cancers.[2] The 2016 IARC update on body fatness and cancer concluded that the evidence was sufficient to conclude that avoiding excess body fatness lowers the risk of multiple myeloma but evidence for its lowering the risk of prostate cancer mortality and diffuse large B-cell lymphoma is limited. Thus, for these cancer sites, the committee could not rule out bias and confounding as contributing to the positive associations observed.[2] In addition, excessive weight is a risk factor for cancer mortality overall.[3] To first summarize the current evidence on cause, we placed the greatest emphasis on prospective cohort studies reported as pooled analyses of individual participant data. This approach reduces variation in analytic approaches among studies. Furthermore, for rare cancers such a multiple myeloma, it allows all cohorts to contribute end points regardless of whether they have published results or not, hence reducing the publication bias that can distort meta-analyses limited to results already published in the literature. In this review, we summarize studies on obesity and the incidence of prostate, hematologic, and renal cancers. We are not aware of any randomized controlled trials of weight-loss interventions after diagnosis of cancer at these sites. We summarize the observational evidence on adiposity/obesity and cancer prognosis in Table 1, and describe associations for each included cancer site in greater detail.

Table 1. Summary of Observational Studies on Adiposity/Obesity and Cancer Prognosis

Cancer type	Prospective Cohort*	Patient Cohort† and Retrospective Cohort‡
Prostate cancer		
Cancer-specific survival	Meta-analysis[4]: RR, 1.15 (95% CI, 1.06 to 1.25) per 5 kg/m^2 increased BMI	Meta-analysis[4]: RR, 1.20 (95% CI, 0.99 to 1.46) per 5 kg/m^2 increased BMI
Hematologic malignancies		
Lymphoma		
Cancer-specific survival	Meta-analysis[5]: RR, 1.14 (95% CI, 1.04 to 1.26) per 5 kg/m^2 increased BMI	
Leukemia		
Overall survival	Meta-analysis[6]: RR, 1.29 (95% CI, 1.11 to 1.49) in obese (BMI ≥ 30 kg/m^2) *v* normal- weight (18.5 kg/m^2 ≤ BMI < 25 kg/m^2) patients RR_{men}, 1.45 (95% CI, 1.22 to 1.72) RR_{women}, 1.14 (95% CI, 0.99 to 1.33)	Pooled patient cohort[7]: HR, 1.72 (95% CI, 1.15 to 2.58) in obese (BMI ≥ 30 kg/m^2) *v* nonobese (BMI < 30 kg/m^2) patients with APL
Relapse		Cohort of patients with APL[8]: HR, 2.45 (95% CI, 1.00 to 5.99) in overweight/obese (BMI ≥ 25 kg/m^2) *v* under-/normal-weight (BMI < 25 kg/m^2) patients
Pediatric leukemia		
Overall survival		Meta-analysis[9]: HR, 1.30 (95% CI, 1.16 to 1.46) in obese (BMI > 95%) *v* nonobese (BMI ≤ 95%) patients
Event-free survival		Meta-analysis[9]: HR, 1.46 (95% CI, 1.29 to 1.64) obese (BMI > 95%) *v* nonobese (BMI ≤ 95%) patients
Multiple myeloma		
Cancer-specific survival	Meta-analysis[10]: RR, 1.15 (95% CI, 1.04 to 1.27) in overweight (25.0 kg/m^2 ≤ BMI < 30 kg/m^2) patients; RR, 1.54 (95% CI, 1.35 to 1.76) in obese (BMI ≥ 30 kg/m^2) *v* normal-weight (18.5 kg/m^2 ≤ BMI < 25 kg/m^2) patients Pooled analysis[11]: HR, 1.09 (95% CI, 1.03 to 1.16) per 5 kg/m^2 increased cohort-entry BMI; HR, 1.22 (95% CI, 1.09 to 1.35) per 5 kg/m^2 increased early-adulthood BMI; HR, 1.06 (95% CI, 1.02 to 1.10) per 5 cm increased waist circumference.	
Kidney cancer		
Overall survival		Patient cohort[12]: HR, 0.50 (95% CI, 0.31 to 0.81) in obese (30 kg/m^2 ≤ BMI < 35 kg/m^2) patients; HR, 0.24 (95% CI, 0.09 to 0.60) in severely obese (BMI ≥ 35 kg/m^2) *v* nonobese (BMI kg/m^2 < 30 kg/m^2) patients Meta-analysis of retrospective studies[13]: HR, 0.57 (95% CI, 0.43 to 0.76) in highest *v* lowest BMI category
Cancer-specific survival	Million Women cohort[14]: RR, 1.65 (95% CI, 1.28 to 2.13) per 10 kg/m^2 increased BMI	Patient cohort[15]: HR, 0.87 (95% CI, 0.82 to 0.94) per 1 kg/m^2 increased BMI in patients with clear cell variant; HR, 1.32 (95% CI, 1.03 to 1.70) per 1 kg/m^2 increased BMI in patients with chromophobe variant; no association in patients with papillary variant Meta-analysis of retrospective studies[13]: HR, 0.59 (95% CI, 0.48 to 0.74) in highest *v* lowest BMI category
Recurrence-free survival		Meta-analysis of retrospective studies[13]: HR, 0.49 (95% CI, 0.30 to 0.81) in highest *v* lowest BMI category

Abbreviations: APL, acute promyelocytic leukemia; BMI, body mass index; HR, hazard ratio; RR, relative risk.
*Cancer-free at cohort entry, BMI measured before diagnosis.
†BMI measured at diagnosis.
‡BMI measured after diagnosis.

OBESITY AND INCIDENCE OF PROSTATE, HEMATOLOGIC, AND RENAL CANCERS

There is no clear link between obesity and overall prostate cancer incidence. A meta-analysis of 27 cohorts estimated the association between obesity and prostate cancer risk, reporting a relative risk of 1.03 [95% CI, 1.00 to 1.07] per 5 kg/m^2 increase in BMI (P = .11) with varied results across cohort studies.[16] A growing body of research indicates that obesity is associated with an increased risk of advanced prostate cancer.[17,18] The IARC update concluded that the evidence for an association between excess body weight and fatal prostate cancer was limited.[2] Meta-analytic data of prospective cohort studies suggest a modest but consistent direct effect of BMI on the incidence of lymphoma, multiple myeloma, and adult leukemia.[16,5,10,19] Risk increases in a dose-response fashion. It is also important to note that the adverse impact of BMI on the risk of lymphoma and multiple myeloma may start growing early, during young adulthood. On the basis of a review of the evidence, the IARC stated in 2016 that the evidence was sufficient to conclude that an absence of excess body fatness lowers the risk of multiple myeloma. Mounting evidence for kidney cancer continues to show increasing risk with increasing BMI in a dose-response fashion.[16,20,21]

OBESITY AND PROSTATE CANCER PROGNOSIS

A growing body of research indicates that obesity is associated with worse pathologic outcomes in prostate cancer; however, evidence of an association has varied across cohort studies. Analysis of 57 European and American prospective studies shows an overall RR of prostate cancer mortality of 1.13 (95% CI, 1.02 to 1.24) for a 5 kg/m^2 increase in BMI.[22] In contrast, in an analysis of Asian cohorts, obesity was not related to prostate cancer mortality.[23] Obesity is linked to hormonal imbalances and hormonal factors that may influence prostate cancer progression.[24,25] Several mechanisms that may contribute to the growth of prostate cancer, including adiponectin levels[26] and inflammatory mediators,[27] have also been explored for relations with survival and mortality.

Epidemiologic studies show that obesity is associated with an increased risk of prostate cancer aggressiveness,[28-32] progression,[32-36] and cancer-specific mortality.[27,32,37-39] Chalfin et al[40] found that obese men are more likely to have worse pathology and a higher risk of recurrence of their cancer. Furthermore, Asmar et al[41] and Ly et al[42] reported that increased BMI was significantly associated with a higher risk of biochemical failure.

Incidence rates for prostate cancer are 60% higher for African-American men,[43] who also have the highest prostate cancer mortality. Prostate cancer accounts for 44% of the overall cancer mortality disparity between African-American and white men.[44] Studies suggest that obesity may contribute to this disparity in prostate cancer outcomes.[31,4,45-47] African-American men have higher rates of obesity compared with white men.[48] Obesity is also associated with both prostate tumor biology and a delayed prostate-specific antigen diagnosis of prostate cancer. Studies have also found that in men with low-risk disease, obese African-American men have a higher risk of recurrence compared with obese white men.[49]

Although physical activity, especially vigorous activity, is inversely related to the incidence of aggressive prostate cancer[50-56] and may also be associated with a decreased overall incidence of prostate cancer,[57] associations between obesity and prostate cancer seem to be independent of the level of physical activity.

Continued study is warranted to clarify the associations reported to date and to identify additional factors that may modify the relationship between obesity and prostate cancer prognosis. Short follow-up and lack of control for smoking are major limitations in many of these studies, especially in data from clinical studies. Other neglected areas of study include the timing of BMI measurements (eg, 1, 2, or 5 years before prostate cancer diagnosis) and the ability to assess ethnic disparities, including the association between obesity and lethal prostate cancer in African-American and other minority groups.

OBESITY AND HEMATOLOGIC MALIGNANCIES PROGNOSIS

Epidemiologic evidence from prospective cohort studies indicates does-response associations between excessive body weight and an increased risk of mortality from several subtypes of hematologic malignancies.[16]

The most recent meta-analysis of BMI and lymphoma by Larsson and Wolk[5] summarized available prospective data through May 2011, including five studies (n = 3,407 cases) of BMI in relation to non-Hodgkin lymphoma (NHL) mortality. A does-response association between increasing BMI and increased NHL mortality was observed. Per 5 kg/m^2 increase in BMI, the RR of NHL mortality was 1.14 (95% CI, 1.04 to 1.26). Conversely, some studies have reported that a higher BMI is associated with better survival outcomes in retrospective data.[58,59] In a more recent study, Hwang et al[60] reported data for Asian patients with diffuse large B-cell lymphoma and noted worse overall survival (hazard ratio [HR], 1.29; 95% CI, 1.08 to 7.95) and worse progression-free survival (HR, 2.59; 95% CI, 1.06 to 6.35) in the obese. Similarly, Leo et al[61] observed an association between obesity and worse NHL-specific survival in patients of diverse ethnicities (HR, 1.77; 95% CI, 1.30 to 2.41). One prospective study in Taiwan included a measure of central obesity (defined as waist circumference $\geq$ 90 cm in men, $\geq$ 80 cm in women) and reported worse NHL-specific survival in centrally obese patients (HR, 2.16; 95% CI, 1.41 to 3.31) after adjusting for BMI.[62] Across these studies, a worse prognostic outcome in underweight patients was reported, consistent with the impact of the disease process on weight.[60,63,64]

Multiple myeloma is relatively rare compared with lymphoma or leukemia; it has historically poor survival, with a 5-year survival rate of $<$ 50% in the United States.[65] Both overweight and obesity are associated with multiple myeloma mortality. Wallin and Larsson[10] combined available data restricted to prospective cohort studies published up to 2011. Data from five prospective cohorts (n = 1,845 cases) suggested worse overall survival in both overweight (RR, 1.15; 95% CI, 1.04 to 1.27) and obese (RR, 1.54; 95% CI, 1.35 to 1.76) patients with multiple myeloma. These associations, assessed as a dose-response per 5 kg/m^2 increase in BMI, gave a 21% increased risk of multiple myeloma mortality per 5 kg/m^2 increase in BMI. The most updated pooled analysis of individual participant data from 20 prospective studies[11] extended the analysis on multiple myeloma mortality, including the association of early-adulthood BMI and weight distribution. BMI at cohort entry (RR, 1.09 [95% CI, 1.03 to 1.16] per 5 kg/m^2) and higher early-adulthood BMI (RR, 1.22 [95% CI, 1.09 to 1.35] per 5 kg/m^2) were both associated with increased multiple myeloma mortality. In this combined analysis, waist circumference (HR, 1.06 [95% CI, 1.02 to 1.10] per 5 cm) was also associated with mortality, suggesting the deleterious impact of central obesity. The association between early-adulthood BMI and mortality was stronger in women (HR, 1.95 [95% CI, 1.33 to 2.86] for BMI > 25 kg/m^{2}compared with BMI of 18.5 to 25 kg/m^2).

Leukemia accounts for 2.5% of all cancer cases globally.[66] Among its four major types, acute lymphoblastic leukemia (ALL) is the most common tumor in children, whereas other subtypes (chronic lymphocytic leukemia, acute myeloid leukemia, and chronic myeloid leukemia) occur mostly later in adult life. In adult populations, obesity is associated with a higher risk of leukemia mortality (RR, 1.29; 95% CI, 1.11 to 1.49) on the basis of data from six prospective cohort studies (n = 2,358 deaths) up to 2011.[6] The association between elevated BMI and leukemia mortality was linear in both men (1.9% per kg/m^2, P = .10) and women (1.2% per kg/m^2, P = .01). Several studies were conducted with retrospective design after the meta-analysis. Wenzell et al[67] reported improved overall survival in obese patients with leukemia, but others reported null findings.[68,69] A recent analysis that pooled data from four Cancer and Leukemia Group B (Alliance) clinical trials of patients with acute myeloid leukemia, including acute promyelocytic leukemia (APL), linked obesity to worse overall survival (HR, 1.72; 95% CI, 1.15 to 2.58) and disease-free survival (HR, 1.53; 95% CI, 1.03 to 2.27) in APL, but not in non-APL, suggesting a possible distinct biologic relation between obesity in APL.[7]

Studies of childhood leukemia have been focused mostly on ALL, the most common tumor in children. Data on other subtypes of childhood leukemia are scarce. Amankwah et al[9] conducted a meta-analysis synthesizing data from 11 studies up to 2015 to access the association between obesity at diagnosis and pediatric (< 21 years old) acute leukemia survival and relapse. They reported worse overall survival (HR, 1.30; 95% CI, 1.16 to 1.46) and worse event-free survival (HR, 1.46; 95% CI, 1.29 to 1.64) in patients who were obese at diagnosis. When the analysis was restricted to ALL only, both these associations persisted and were stronger (HR, 2.25 [95% CI, 1.33 to 3.82] for overall survival; and HR, 1.49 [95% CI, 1.30 to 1.71] for event-free survival).

Current evidence suggests a modest but consistent direct effect of BMI on poor prognostic outcomes in lymphoma, multiple myeloma, and leukemia. Risk increases in a dose-response manner in several subtypes of hematologic malignancies. It is also important to note that the adverse impact of BMI on multiple myeloma prognosis may reflect etiologic risk that starts growing early, during young adulthood. Separating the etiologic effect, disease severity at diagnosis, and outcomes requires more evidence from randomized interventions. To date, the small number of prospective studies and the lack of adjustment for possible confounding factors such as treatment, smoking, and comorbidities may bias the estimates reported for mortality as a result of hematologic malignancies.

OBESITY AND RENAL CANCER PROGNOSIS

Renal cancer (predominantly renal cell carcinoma [RCC]) accounts for approximately 2% of new cancer diagnoses. The IARC review in 2002 included evidence from four cohort studies and concluded a consistently positive association,[1] as did the World Cancer Research Fund review in 2007[70] and the subsequent update in 2015. The IARC 2016 update continues to classify RCC as caused by obesity.[2] Obesity is, however, associated with improved prognosis in patients with RCC, supported by a 2013 systematic review. This meta-analysis included data from 20 studies and reported improved overall (HR, 0.57; 95% CI, 0.43 to 0.76), cancer-specific (HR, 0.59; 95% CI, 0.48 to 0.74), and recurrence-free (HR, 0.49; 95% CI, 0.30 to 0.81) survival in patients with higher BMI than in those with lower BMI.[13] Notably, all these studies used a retrospective design. Data from prospective cohorts of patients are generally sparse. A 2016 study analyzed data from a prospective randomized trial of 845 localized high-risk patients with RCC and reported that a higher BMI was associated with improved survival.[12] The UK Million Women Study cohort found worse kidney-specific survival (RR, 1.65; 95% CI, 1.28 to 2.13) for every 10 kg/m^2 increment in cohort entry BMI, and the risk with increasing BMI was stronger in never-smokers.[71] Recently, a Korean patient cohort of 2,769 cases investigated the association between BMI and prognosis of nonmetastatic RCC by histologic subtype.[15] This study reported that a higher BMI (≥ 23 kg/m^2) was associated with improved cancer-specific survival (HR, 0.87) in patients with the clear cell variant, but worse cancer-specific (HR, 1.32) and recurrence-free (HR, 1.32) survival in patients with the chromophobe variant. No association was seen in patients with the papillary variant.[15] The association between obesity and RCC prognosis thus may differ by histologic subtype, although further study is needed to confirm these associations.

Current evidence on RCC prognosis is based mostly on data generated by retrospective studies, with few data available from prospective cohorts. These data support an obesity paradox in patients with RCC with the clear cell variant. That is, although obesity is an established risk factor for RCC, being obese at diagnosis seems to be associated with a favorable outcome compared with the outcomes of patients with normal weight at diagnosis. Some studies have reported that obese patients are more likely to be diagnosed with favorable clinical characteristics, including lower-stage disease, lower Fuhrman grade, and smaller tumors, compared with normal-weight patients.[13] Further support from gene expression analyses demonstrates that obese patients are less likely to have a tumor with fatty acid synthase (FASN), which encodes the proteins necessary for tumor growth.[72]

OBESITY AND CANCER PROGNOSIS MECHANISMS

The mechanisms of obesity in relation to cancer development and prognosis are poorly understood on the basis of current studies. Furthermore, determining how much of an outcome is attributable to obesity, treatment, or the underlying disease subtypes/biology is difficult. It has been proposed that chemotherapy dosing that is based on body surface area in obese patients may be biased and may result in poor survival. Hourdequin et al[73] conducted a meta-analysis and reported similar or lower levels of toxicity in obese patients compared with normal-weight patients when they received body surface area–based chemotherapy dosing, and no differences in survival outcomes were seen. Obesity reflects increased adipose tissue, which secretes a range of adipokines that may play a role in cancer development. These adipokines include inflammatory cytokines such as tumor necrosis factor-α and interleukin-6, which likely cause a chronic inflammatory microenvironment that also promotes cancer progrssion.[74] Such inflammation may lead to the activation of transcription factor nuclear factor-kB, which is linked to several cancers, including lymphoma.[75] Adipose tissue secretes leptin and adiponectin, which are both linked to prostate cancer and RCC.[75] Other pathways associated with obesity, such as hyperinsulinemia, insulin-insulin-like growth factor signaling, and lipid levels, have been explored in relation to cancer progression. For example, downgraded expression of FASN was found in obese patients with RCC and was associated with an improved survival.[72] In patients with prostate cancer, overweight men carrying a variant FASN allele had a poorer prognosis compared with men of normal weight.[76] These possible pathways require further research to address the potential response to weight loss after cancer diagnosis and possible improvement in survival outcomes. The cancer sites in this review have less evidence for a benefit of weight loss after diagnosis than is currently accumulating for breast and colorectal cancer.

CLINICAL RECOMMENDATIONS

At the current time, the rapidly rising prevalence of obesity in all age groups may contribute to a large future cancer burden. The American Society of Clinical Oncology established a multipronged initiative and committed to reducing the impact of obesity on cancer.[77] The delivery of effective and efficient counseling on weight-management strategies, however, might be challenged by the poor understanding of the relationship between obesity and cancer progression. Cancer survivors are encouraged to achieve and maintain a healthy weight. Guidelines from the American Cancer Society[78] and the American College of Sports Medicine[79] suggest that cancer survivors should follow the physical activity guidelines for Americans, with specific exercise programming adaptations on the basis of disease- and treatment-related adverse effects (ie, ≥ 150 minutes per week of moderate-intensity physical activity). In addition, cancer survivors are encouraged to achieve a high intake of vegetables, fruits, and whole grains and to avoid high-calorie foods and beverages. It is still unclear what impact specific lifestyle components (energy intake/diet or energy expenditure/physical activity) that contribute to obesity have in relation to cancer progression. With limited prospective longitudinal data on weight change in relation to prognostic outcomes, and in the absence of randomized controlled trials, cancer survivors should probably not be advised to voluntarily lose weight to reduce cancer recurrence or mortality. Yet maintaining a healthy lifestyle through physical activity, healthy diet, and avoiding weight gain may lead to general health benefits beyond cancer-specific outcomes.

FUTURE DIRECTIONS

Future research to advance the understanding of weight management in the cancer care continuum can help document the time course of weight loss and improved outcomes after diagnosis and identify pathways that may be addressed more directly through drug therapies. Given the association between obesity and cancer incidence and mortality, shifting the perspective of clinical oncology practice to include weight management as a component of primary and secondary prevention of cancer is increasingly important.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Obesity and Other Cancers

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