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Are findings from studies of obesity and prostate cancer really in conflict?

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Abstract Recent studies on the association between obesity and prostate cancer appear to be in conflict. A recent prospective cohort study reported that the incidence of prostate cancer was lower among obese men under the age of 60 years and among those men with a family history of prostate cancer. Similarly, a case–control study found obesity was inversely associated with prostate cancer risk in men aged 40–64 years. However, several prospective cohort studies found that obese men are more likely to die from prostate cancer than non-obese men. Finally, two recent studies found that among men with prostate cancer, obese men were more likely to have a biochemical progression after surgery. We postulate that by closely examining the comparison groups used in these studies, these findings may, in fact, be in agreement. Specifically, this paradox within the literature may result from the possibility that obesity influences the development of aggressive (*i.e.*, higher stage, higher grade, recurrence, death) and non-aggressive disease differently. We suggest that obesity may reduce the risk of non-aggressive disease but simultaneously increase the risk of aggressive disease. Finally, additional methodological issues are discussed that investigators need to be aware of to be able to draw inferences across studies of obesity and prostate cancer outcomes.

Keywords Aggressiveness · Body mass index · Incidence · Obesity · Prostate cancer

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Commentary

There appears to be a paradox in recent epidemiologic findings on the association of obesity with prostate cancer incidence and aggressiveness [1]. A recent prospective cohort study of men in the United States without a diagnosis of prostate cancer at baseline, reported that the incidence of prostate cancer was lower among obese men under the age of 60 years and among those men with a family history of prostate cancer, though there were no differences in the incidence of total prostate cancer overall or advanced disease [2]. Similarly, a case–control study from the United States also suggested an inverse association between obesity and total prostate cancer incidence among men aged

40–64 years at diagnosis [3]. Conversely, other studies have recently reported that among men undergoing radical prostatectomy for early stage prostate cancer, obese men were more likely to have high-grade disease [4–6] and biochemical progression following surgery [4, 5], suggesting more aggressive disease among obese men. In addition, several prospective cohort studies found that men with a higher body mass index were at increased risk of prostate cancer death [7–9]. On the surface, these results appear to conflict. However, by more closely examining the comparison groups used in these studies, we postulate that these findings may, in fact, be in agreement.

In prospective cohort and case–control studies of prostate cancer *incidence*, the comparison group is men without a diagnosis of prostate cancer (or the population at risk) who have the exposure distribution of the population that gave rise to the cases. In contrast, some prospective cohort or case–control studies of prostate cancer *aggressiveness* and *recurrence* use men with non-aggressive prostate cancer as the reference group. However, men with non-aggressive prostate cancer, by virtue of already having the exposure-associated disease (prostate cancer), may not have the same exposure distribution as the population that gave rise to the aggressive prostate cancer cases. This difference in the nature of the comparison group is an important distinction that may possibly underlie the apparent conflict among the results from epidemiologic studies of prostate cancer incidence *versus* aggressiveness/recurrence. Both of these comparison groups are valid, depending on the specific research question, and findings from studies using either type of comparison group are very useful in identifying and characterizing the associations between obesity and prostate cancer outcomes. However, investigators need to be aware of this methodological issue to be able to draw inferences across studies of obesity and prostate cancer outcomes.

This methodological issue of the nature of the comparison group arises from the possibility that obesity may differentially affect the development of non-aggressive and aggressive prostate cancer. Among men, obesity is associated with lower serum androgenicity [10]. Prostate cancers are very sensitive to androgenic activity, and it has been proposed that testosterone may be necessary for tumor development [11]. However, testosterone also helps to maintain the differentiated state of normal prostatic epithelium and may play a similar role to help maintain tumor differentiation [12]. Therefore, the net effect of lower androgenic activity among obese men may be a reduced overall risk of prostate cancer, but an increased risk of development of poorly differentiated cancers. Indeed, several recent clinical reports support a link between more aggressive prostate cancers developing in men with lower serum testosterone concentrations [13–16]. In addition, epidemiological reports including a prospective cohort study [17] and a randomized trial of inhibition of intraprostatic dihydrotestosterone formation *via* the drug, finasteride [18], both found more high-grade tumors among cases with lower androgenicity. Moreover, obesity is associated with other factors such as caloric excess, high-fat diet, and alterations in multiple serum hormones including estrogen, insulin, leptin, and free insulin-like growth factor-1 that may all promote the development and progression of aggressive prostate cancer.

To illustrate the influence of differing comparison groups on the results of clinical and epidemiological studies examining obesity and prostate cancer incidence and aggressiveness/progression, we present the following scenarios under which obesity may influence the development of aggressive (*i.e.*, higher stage, higher grade, recurrence, death) and non-aggressive disease differently:

(1) Obesity increases the risk of aggressive disease, but does not affect the risk of non-aggressive disease.
(2) Obesity does not affect the risk of aggressive disease, but decreases the risk of non-aggressive disease.
(3) Obesity increases the risk of aggressive disease, but decreases the risk of non-aggressive disease.

Now consider Table 1. In each scenario the prevalence of obesity in the controls (or in the population at risk) is 30%. We varied the prevalence of obesity in the cases as well as the proportion of cases that are aggressive. We selected three prevalences of aggressive disease: 60% to correspond to that typically observed in the pre-PSA era (prior to widespread PSA testing of asymptomatic men) and in countries that currently have virtually no use of PSA screening; 40% to correspond to that typically observed in the early-PSA era and in countries that currently have low use of PSA screening and 20% to correspond to the PSA-era in countries with widespread PSA screening. We present both odds ratios (OR) that would be estimated in a case–control study and risk ratios (RR) that would be estimated in a cohort study. In the first scenario, the risk of aggressive disease is increased among obese men with no effect on the risk of non-aggressive disease. This scenario results in a modest increase in the overall prostate cancer risk among obese men, but a much more dramatic increase in the risk of aggressive disease relative to controls (or the population at risk) or to non-aggressive disease. Note that the prevalence of aggressive disease (20% *versus* 40% *versus* 60% in the sensitivity analysis) influences the magnitude of the OR (or the RR) of overall prostate cancer. While this scenario would fit with the results from studies that found an increased risk of total prostate cancer incidence [19, 20] as well as high-grade disease [4–6] and biochemical progression following surgery [4, 5] and increased risk of prostate cancer death [7–9] among obese

Table 1 Influence of the nature of the comparison group (controls or non-aggressive cases as controls) on the association of obesity with prostate cancer and aggressive disease/recurrence under three biological scenarios

	Prevalence of aggressive disease	Prevalence of obesity				Odds ratio (risk ratio) of prostate cancer comparing obese *versus* non-obese			
		Controls (or population at risk)	Aggressive disease	Non-aggressive disease	Weighted average among all cases	*versus* controls (or population at risk)			*versus* non-aggressive disease as controls
						All cases	Aggressive disease	Non-aggressive disease	Aggressive disease
Scenario 1: Obesity increases risk of aggressive prostate cancer, but does not affect risk of non-aggressive disease									
A*	0.60	0.30	0.40	0.30	0.36	1.31 (1.17)	1.56 (1.33)	1.00 (1.00)	1.56 (1.33)
B**	0.40	0.30	0.40	0.30	0.34	1.20 (1.13)	1.56 (1.33)	1.00 (1.00)	1.56 (1.33)
C***	0.20	0.30	0.40	0.30	0.32	1.10 (1.07)	1.56 (1.33)	1.00 (1.00)	1.56 (1.33)
Scenario 2: Obesity does not affect risk of aggressive disease, but decreases risk of non-aggressive prostate cancer									
A	0.60	0.30	0.30	0.22	0.27	0.85 (0.89)	1.00 (1.00)	0.64 (0.72)	1.56 (1.39)
B	0.40	0.30	0.30	0.22	0.25	0.78 (0.83)	1.00 (1.00)	0.64 (0.72)	1.56 (1.39)
C	0.20	0.30	0.30	0.22	0.23	0.71 (0.78)	1.00 (1.00)	0.64 (0.72)	1.56 (1.39)
Scenario 3: Obesity increases the risk of aggressive disease, but decreases the risk of non-aggressive disease									
A	0.60	0.30	0.40	0.22	0.33	1.13 (1.09)	1.56 (1.33)	0.64 (0.72)	2.42 (1.85)
B	0.40	0.30	0.40	0.22	0.29	0.95 (0.97)	1.56 (1.33)	0.64 (0.72)	2.42 (1.85)
C	0.20	0.30	0.40	0.22	0.25	0.79 (0.84)	1.56 (1.33)	0.64 (0.72)	2.42 (1.85)

*A corresponds to the pre-PSA era or in countries with virtually no PSA screening when approximately 60% of all newly diagnosed cases were classified as aggressive lesions

**B corresponds to the early-PSA era or in countries without widespread PSA screening when approximately 40% of all newly diagnosed cases were classified as aggressive lesions

***C corresponds to the PSA era (current) in countries with widespread PSA screening when approximately 20% of all newly diagnosed cases were classified as aggressive lesions

men, it does not fit with the findings from the recent prospective cohort study which found that the incidence of early-stage prostate cancer was lower among obese men under the age of 60 years and among those men with a family history of prostate cancer [2] nor the case–control study that showed an inverse association between body mass index and total incident prostate cancer [3].

In the second scenario obesity does not affect the risk of aggressive disease, but decreases the risk of non-aggressive disease. The result is a reduced risk of both non-aggressive and overall prostate cancer cases relative to controls (or the population at risk). However, when calculating the risk of aggressive disease relative to men with non-aggressive disease, the OR (or RR) is greater than 1 (increased risk). Thus, despite obesity having no direct effect on the development of aggressive disease in scenario 2, there is an apparent enrichment of obese men with aggressive disease when men with non-aggressive disease are used as the comparison group. Note that this scenario would account for the apparent disparate results between the cohort study of prostate cancer incidence (inverse association for obesity and prostate cancer in young men or men with a family history) [2] and the case–control study which found an inverse association between body mass index and total prostate cancer incidence [3] as well as the studies in men treated with radical prostatectomy (positive association for obesity and prostate cancer aggressiveness/recurrence) [4–6], though this would conflict with the prospective population-based cohort studies showing an increased risk of prostate cancer death among obese men [7–9].

In the third scenario obesity increases the risk of aggressive disease, but decreases the risk of non-aggressive disease. In this scenario the risk of overall prostate cancer is highly dependent on the prevalence of aggressive disease. When the prevalence of aggressive disease is 60%, obesity is associated with an *increased* risk of total prostate cancer incidence. However, when the prevalence of aggressive disease is 40%, a minimal association is apparent between obesity and overall prostate cancer risk and when the prevalence of aggressive disease is 20%, obesity is inversely associated with overall prostate cancer risk. Also, note that the OR (or RR) of aggressive disease is much higher when compared to non-aggressive disease than when compared to controls (or the population at risk). This third scenario would best account for the findings in each of the types of analyses published to date. First, it would account for an inverse association between obesity and incident total prostate and early stage in subgroups in a prospective population-based cohort study of prostate cancer incidence [2] and in the case–control study [3] in the United States due to decreased incidence of non-aggressive disease (scenario 3A). In addition, due to greater incidence of aggressive disease, this scenario would account for the positive association between obesity and high-grade disease or recurrence in studies of in men treated with radical prostatectomy [4–6], and a positive association between obesity and prostate cancer death in prospective population-based cohort studies [7–9]. Moreover, this scenario would account for the positive association between obesity and total prostate cancer incidence seen in studies prior to the PSA era or those in countries where PSA screening was extremely low (scenario 3C) [19, 20]. The only aspect not consistent with this third scenario is the lack of an association between obesity and aggressive disease in the prospective population-based cohort study of prostate cancer incidence [2], although the number of advanced cases in that study was too few to obtain a stable estimate of whether or not obesity was associated with advanced disease.

These scenarios support the notion that the nature of the comparison groups (men without prostate cancer *versus* men with prostate cancer but with non-aggressive disease) used in epidemiological studies investigating the association between obesity and prostate cancer incidence and aggressiveness/recurrence potentially produces apparent discrepancies in the results when the biological association between obesity and development of aggressive and non-aggressive disease differs. In addition, differing prevalences of aggressive disease among prostate cancer cases in study populations drawn from times and places differing on the extent and use of prostate cancer screening, as well as the known overestimation of the RR by the OR when the risk of the disease is high in the source population (*e.g.*, when comparing aggressive to non-aggressive disease and thus, the source population is men with prostate cancer – see OR *versus* RR estimate in Table 1), contributes to the apparent conflict in results.

It should be noted that we cannot exclude the possibility that alternative non-biological explanations may also contribute to the apparent disparate results among epidemiological studies of prostate cancer incidence and aggressiveness. For example, there may be differential detection of cancers in obese and normal weight men. Detection bias may result from differences in the extent to which obese and normal weight men are screened for prostate cancer, and the clinical characteristics of obese men that may influence the likelihood of detecting a cancer (larger prostate size, possibly lower serum PSA concentration, etc.) [21, 22]. Of note, if there were an inherent bias against detection of early-stage cancers in obese men, the corollary would be that when a cancer is detected in obese men, the cancer would be more advanced. This would result in a situation similar to scenario 3 (Table 1), but for which the lower risk of non-aggressive disease would not be causal but due to detection bias.

Variability in results for early-stage disease may also be caused by biologic factors, such as the age distribution of the

cases being studied. In the prospective population-based cohort study of prostate cancer incidence [2], the reduced risk of prostate cancer was only observed among men younger than 60 years old. Similarly, the case–control study from the United States, which found an inverse association between body mass index and prostate cancer risk only examined data from men aged 40–64 at diagnosis. Therefore, it is possible that the reduced androgen concentrations associated with obesity might be more relevant for younger men who have higher baseline levels of circulating androgens than for older men.

A final consideration is that the relationship between obesity and progression among men with early stage disease may be influenced by primary therapy, which may be less effective in obese men due to technical difficulties during surgery resulting in increased risk of positive surgical margins [5] or setup error during external beam radiation therapy reducing the dose delivered to the prostate [23]. Importantly though, the increased risk of positive surgical margins among obese men undergoing surgery accounted for some but not entirely for the increased risk of progression after surgery in one study [5].

The relationship between obesity and prostate cancer is likely complex. It is important to continue to test hypotheses about obesity and prostate cancer in other epidemiological studies with detailed information on the pathologic characteristics of the cases and long-term follow-up. In addition, basic science investigations into possible mechanisms that would link obesity to increased development and progression of prostate cancer should be done. Ultimately, these future studies are needed so that a unified picture of the influence of obesity on prostate cancer development and progression can be obtained. This big-picture view will allow the development of a standardized public health message concerning the association between obesity and prostate cancer.

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