Obesity and prostate cancer

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The relationship between obesity and prostate cancer is currently a hotly debated topic, but despite the number of publications devoted to the topic, the actual nature of the relationship remains uncertain. Obesity has been shown to have a direct relationship with the incidence of prostate cancer in a number of studies but an equal number of studies have shown no association. The relationship is further obscured with recent findings that obesity in younger obese men may actually be protective against prostate cancer. Confounding factors include the lack of correlation of body mass index (BMI) as a measure of central obesity and the lack of consistency in timing of BMI measurements, i.e. before or after diagnosis and in young or advanced adulthood. Evidence for increased BMI as a risk factor for prostate cancer is unclear, but less ambiguous is the mounting substantiation that obesity is associated with prognostically worse disease, poorer post-surgical outcomes and increased prostate cancer mortality, irregardless of margin status. From a biologic perspective, one can put forth a number of potential mechanisms by which obesity might promote prostate cancer and/or prostate cancer progression including; low levels of testosterone, increased levels of estrogen, co-existing diabetes or metabolic syndrome, increased circulating insulin-growth factor-one (IGF-1), increased levels of leptin, decreased levels of adiponectin and increased dietary saturated fats. Evidence for the association of these factors with prostate cancer are examined herein. The timing of serum measurements is crucial in elucidating whether these factors have causative influence on prostate cancer or rather are produced by the prostate cancer cells and are better understood as markers of disease. The interaction between obesity and prostate cancer is important to clarify because it will have impact on the prevention, prognostication and treatment of prostate cancer. Future study with careful attention to avoid the methodological pitfalls of the past need be accomplished to bear out the nature of the interaction of obesity and prostate cancer.

Key Words: obesity, prostate cancer, risk factors, hypogonadism, leptin, adiponectin, IGF-1

Introduction

The relationship between obesity and prostate cancer is currently a hotly debated topic. Despite the number of publications devoted to the topic, the actual nature of the relationship remains uncertain. Obesity, typically defined as a body mass index (BMI) of greater than 25, has been implicated as a risk factor for the development of prostate cancer as well as a predictor of worsened biologic outcome for the disease. While several studies support these hypotheses, a number exist to refute them as well.

Several obstacles exist in the study of obesity as a risk factor for prostate cancer. The vast majority of studies evaluating the relationship of obesity and prostate cancer have utilized BMI as the measure of obesity. Investigators have recently demonstrated that when studying the relationship of obesity and myocardial infarction (MI), BMI is not an accurate predictor of risk.[1] Alternatively, the use of waist measurement, or waist-to-hip ratio, may be the best predictor of MI risk. Studies utilizing WHR in the study of prostate cancer remain to be done.

The timing of obesity within the course of a man's life may influence prostate cancer risk differentially. Individuals who are obese, and secondarily hypogonadal, at a young age may be at a lower risk than non-obese patients, while those who are obese later in life may have an increased risk. BMI is also confounded by when in the course of disease it is measured. In case control studies BMI is measured after the diagnosis of prostate cancer which may result in erroneously low measures. Additionally confounding the evaluation of obesity as a prostate cancer risk factor are the diet and lifestyle associated with obesity, which may independently contribute risk.

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Biologic basis for obesity as a prostate cancer risk factor

From a biologic perspective, one can put forth a number of potential mechanisms by which obesity might promote prostate cancer and/or prostate cancer progression.

Testosterone

An inverse relationship exists between serum testosterone levels and obesity. Although early studies on animal models demonstrated prostate cancer cell proliferation in response to high level androgen exposure,[2] recent in vivo studies have shown that a reduction in testosterone or hypogonadism has been associated with an increased overall risk of prostate cancer and advanced disease at diagnosis.[3-6] Some of the difficulty in defining the exact nature of this relationship is related to the role of androgens in initiating PSA transcription. Because androgens are necessary for the production of PSA,[7] a hypogonadal state may result in an artificially lowered serum PSA relative to a given prostate size or volume and hence delay in diagnosis. This suggests that correction of serum PSA for testosterone is necessary in order to establish the true risk of prostate cancer in a hypogonadal man.

Estrogen

Increased body fat secondarily results in increased estrogen through peripheral conversion of testosterone to estrogen by aromatase (which is stored in the peripheral fat). Estrogens have a relatively complex impact upon proliferation of prostate cancer cells through pro-proliferative action upon estrogen receptor (ER) alpha and anti-proliferative action upon ER-beta.[8] It is known that in animal models, the presence of testosterone alone will not induce prostate cancer, but the combined presence of testosterone and estrogens will do so.[9,10] It may therefore be the relatively low ratio of testosterone to estrogen that impacts upon the likelihood of carcinogenesis in the prostate. Selective estrogen receptor modulators have been shown to prevent and treat prostate cancer in animal models and are currently being studied in adults.[11]

Diabetes and metabolic syndrome

The incidence of type II diabetes and metabolic syndrome are increased in those with obesity. High circulating levels of insulin and insulin resistance have been associated with an increased risk of prostate cancer.[12-14] Results of studies evaluating the relationship of diabetes and metabolic syndrome to prostate cancer vary from increased risk,[15-17] to no effect,[18-20] to protective effect.[21-24] Studies have been inconsistent in what is considered a diagnosis of diabetes, in documenting the length of disease and in controlling for whether the diabetes is treated and well controlled or not. As early diabetes is associated with high levels of insulin and late disease is associated with lower levels of insulin as the pancreas burns out, it has been theorized and supported by recent studies that diabetes could incur an increased risk of prostate cancer early on, but demonstrate a protective effect later in the disease.[21, 23]

IGF-1

IGF-1 is known to stimulate the growth of prostate cancer cells in culture,[25] and expression of the protein is increased in malignant prostate cells.[26] As such, IGF-1 has been implicated as an etiologic factor in prostate cancer. Several *in vivo* studies suggest a positive correlation between increased IGF-1 levels and prostate cancer.[27-30] These studies are confounded by the observation that men with prostate cancer generally develop an increase in IGF-1 levels, making it unclear if this represents an etiologic factor or a secondary cancer marker.[31] In fact, studies are currently underway which are investigating screening with PSA and IGF-1 levels.

Leptin and adiponectin

Leptin is one of several proteins manufactured by adipocytes which is crucial to energy regulation,[32] and which has been shown to be increased in the serum of obese men.[33] Laboratory studies have demonstrated a stimulatory effect of leptin on angiogenesis and the growth of androgen-independent prostate cancer cells.[34-36] Mixed results regarding the risk of prostate cancer have been observed in case-control studies,[13,37,38] but it appears that higher leptin levels are associated with the presence of more advanced, aggressive cancers.[39,40] Adiponectin is a newly discovered cytokine produced by adipocytes which increases insulin sensitivity and reduces obesity.[41] Low levels of adiponectin and adiponectin receptors are found in obesity[42,43] and this has been linked to a number of obesity-related diseases.[41] High levels of adiponectin have been shown in laboratory studies to inhibit growth of prostate cancer cells even in the presence of leptin or IGF-1 stimulation.[41] It has been postulated that decreases in adiponectin levels may be associated with increased prostate cancer risk in obese men. A recent small study demonstrated significantly lower levels of adiponectin in those with prostate cancer as compared with patients with benign prostatic hypertrophy and healthy controls.[44]

Dietary factors

Obesity is associated with the intake of more saturated fats,[45] which has been shown to promote prostate carcinogenesis in animal models.[46] Increased dietary fat is associated with an elevated risk of prostate cancer and advanced disease as demonstrated by multiple case-control, cohort and prospective studies.[47-51] High fat diet also increases risk of progression of disease and prostate cancer death.[52]

Obesity and prostate cancer risk

The clinical relationship of obesity and prostate cancer has been evaluated in a number of longitudinal cohort studies. To date, results have been quite contradictory. Several studies have demonstrated a positive correlation between increased BMI and the development of prostate cancer, Table 1.[53-56] These studies generally demonstrated the correlation with higher stratiles of BMI. Paradoxically, a recent study

TABLE 1. **Outcomes from studies evaluating risk of prostate cancer attributable to obesity**

Study	Year published	Number of patients	Type of study	Incidence CaP	BMI stratiles	RR
Nilsen et al	1999	22,248	Cohort	2.9%	23.1-24.7	0.80
					24.8-26.2	1.00
					26.3-28.2	0.90
					>/= 28.3	1.00
Schuurman et al	2000	681 cases 1565 controls	Case control	n/a	22-23	1.20
					24-25	1.35
					26-27	1.26
					>/= 28	0.89
Andersson et al	1997	135,006	Cohort	1.8%	22.1-24.1	1.09
					24.2-26.2	1.10
					>26.2	1.13
Veierod et al	1997	25,708	Cohort	0.3%	22.6-24.2	1.00
					24.3-25.6	1.10
					25.7-27.5	0.80
					>/= 27.6	2.20
Engeland et al	2003	951,459	Cohort	3.5%	23.5-24.99	1.04
					25-27.49	1.07
					27.5-29.99	1.07
					30-32.49	1.09
					32.5-34.99	1.15
					>/= 35	0.93
Putnam et al	2000	1,577	Cohort	6.4%	24.1-26.6	1.10
					>26.6	1.60
Giovannucci et al	2003	47,757	Cohort	6.1%	25-27.4	0.82
					27.5-29.9	0.62
					>/= 30	0.64
Bradbury et al	2005	730 cases 2,470 controls	Case control	n/a	25-27.4	0.91*
					27.5-29.9	0.82*
					>/= 30	0.78*
Porter et al	2005	753 cases 703 controls	Case control	n/a	24.5-26.5	1.07*
					26.5-29.1	0.81*
					29.1-55	0.77*

*Actual statistic is odds ratio, not RR
CaP = Prostate Cancer, BMI = Body Mass Index, RR = Relative Risk, CI = Confidence Interval

by Giovannucci et al found an inverse relationship between BMI and the risk of organ confined prostate cancer, but only in patients less than 60 years old who were in the highest stratiles of BMI, suggesting a protective effect of obesity against early prostate cancer in younger obese men.[57] It is hypothesized that the hypogonadism of obesity may be protective against early prostate cancer but have no effect on sporadic cancers acquired later in life. In a case-control study replicating the BMI stratiles used in Giovannucci et al's study an overall decreased risk of prostate cancer for the highest BMI stratiles was observed regardless of age.[58] This trend was also found in a recent large, population-based, case-control study.[59] Other large prospective studies have demonstrated no association between obesity and prostate cancer, Table 1.[47,60,61]

CI 95%	p-value	Finding
(0.6-1.1) (0.8-1.3) (0.7-1.2) (0.8-1.3)	0.77	No association
(0.84-1.73) (0.95-1.9) (0.87-1.83) (0.58-1.37)	0.73	No association
(0.94-1.26) (0.96-1.26) (0.99-1.29)	0.1	No association
(1.4-2.4) (0.5-2.6) (0.3-2) (1.1-4.7)	0.02	Increased risk
(1-1.09) (1.03-1.11) (1.02-1.12) (1.03-1.16) (1.03-1.28) (0.76-1.13)	<0.001	Increased risk
(0.6-1.9) (0.9-2.8)	0.08	Increased risk
(0.67-0.99) (0.46-0.83) (0.45-0.90)	<0.001	Decreased risk
(0.72-1.15) (0.62-1.08) (0.56-1.09)	0.04	Decreased risk
(0.78-1.46) (0.59-1.11) (0.56-1.06)	0.04	Decreased risk

Obesity and radical prostatectomy

Less ambiguous is the relationship of obesity to prostate cancer outcome. A number of studies have suggested worsened disease related outcomes for men with obesity undergoing radical prostatectomy, Table 2.[62-66] One recent prospective study showed that obese men had significantly higher biochemical recurrence rates and significantly shorter times to recurrence, with those men gaining weight between 25 years-old and age of diagnosis at highest risk of early recurrence.[62] Other analyses have revealed higher cancer grades and higher rates of positive margins, extraprostatic spread and lymph node metastasis, resulting in poorer pathological staging in obese patients.[65-67] Observed increased risk of recurrence following surgery in obese men may be partially related to the increased difficulty of the procedure in the obese leading to more positive margins, but the risk remains even when only patients with negative margins are analyzed.[64]

Obesity and prostate cancer mortality

The relationship of obesity to increased risk of prostate cancer death appears clearer and is supported by most studies which have evaluated this outcome, Table 3.[53,68,69] Retrospective study of more than 800,000 men from the American Cancer Society cohorts uncovered increased mortality rates from prostate cancer in obese men up to 36%.[68] Overall prostate cancer mortality rates in obese men are reported to be 21%-49% higher than normal weighted men, with appropriate obesity to risk curves.[70] The greatest relative risk of prostate cancer death is demonstrated when comparing the highest and lowest stratiles of BMI.[53,68]

Conclusions

The relationship of obesity and prostate cancer is complex. A clear biologic rationale exists for the assumption that obesity may promote prostate carci nogenesis and prostate cancer progression. Several studies have supported this assumption. While the relationship of obesity to prostate cancer risk is not clear,

TABLE 2. **Hazard ratios for biochemical recurrence in obesity**

Study	Year published	Number patients	BMI categorization	HR
Strom et al	2005	526	BMI >/= 30 at age 40	2.35
			BMI >/= 30 at dx	1.41
			BMI continuous	1.07*
Amling et al	2004	3162	BMI >/= 30	1.20
Basset et al	2005	2131	BMI >/= 30	1.31
			BMI continuous	1.20*
Freedland et al	2004	1250	BMI 30-35	1.54*
			BMI >/= 35	3.92*
Freedland et al	2004	1106	BMI continuous	1.03
Freedland et al	2005	2880	BMI 30-35	1.51*†
			BMI >/= 35	1.29*†

*Remained significant on multivariate analysis
†Actual statistic relative ratio, not HR
BMI = Body Mass Index, HR = Hazard Ratio

it is quite evident that very obese men have worsened disease-related outcomes when compared to normal weight men. A careful evaluation of the study populations in seemingly conflicting studies, suggests that the study results are useful in uncovering the differential effects of obesity on well and poorly differentiated cancers. Additionally, they may illuminate how large differences in PSA screening practices might conceal existing associations.[71] The relationship between obesity and prostate cancer must be further evaluated in order to determine its impact upon the prevention, prognostication and treatment of

TABLE 3. **Risk of prostate cancer death in obesity**

Study	Year published		Number patients	Number CaP deaths	BMI stratiles	RR	CI 95%	p-value
Andersson et al	1997		135,006	708	22.1-24.1	1.36	(1.03-1.79)	
					24.2-26.2	1.33	(1.02-1.74)	
					>26.2	1.40	(1.09-1.81)	0.04
Rodriguez et al	2001	CPS-I*	381,638	1,590	22.5-24.99	1.04	(0.9-1.2)	
					25-27.49	1.06	(0.91-1.22)	
					27.5-29.99	1.01	(0.84-1.22)	
					30-32.49	1.28	(0.99-1.64)	
					>/= 32.5	1.34	(0.93-1.94)	0.06
		CPS-II*	434,630	3,622	22.5-24.99	0.98	(0.88-1.09)	
					25-27.49	0.99	(0.89-1.1)	
					27.5-29.99	1.11	(0.99-1.26)	
					30-32.49	1.11	(0.94-1.31)	
					>/= 32.5	1.36	(1.11-1.66)	<0.001
Calle et al	2003		65,436	4,004	25-29.9	1.08	(1.01-1.15)	
					30-34.9	1.20	(1.06-1.36)	
					35-39.9	1.34	0.98-1.83)	<0.001

*CPS-I and -II = two large American Cancer Society Cohorts
BMI = Body Mass Index, RR = Relative Risk, CI = Confidence Interval, CaP = Prostate cancer

prostate cancer. Further large studies that carefully consider methodology, such as when and how weight is quantified and timing of measures of proposed related serum substrates, are necessary in order to maximize reproducibility and further elucidate the intricate relationship between obesity and prostate cancer. □

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