News and Views from the Literature

Prostate Cancer

Obesity and Prostate Cancer Detection and Progression

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Obesity is an epidemic in the United States affecting over 30% of the adult population.[1] Obesity is more prevalent among minorities, particularly black men.[2] It has been associated with numerous chronic diseases such as hypertension, cardiovascular disease, and diabetes. It has also been associated with several types of cancers, particularly breast and colon cancer.[3] Recent evidence suggests that obese men have an increased risk of dying of prostate cancer.[4-6] Three recent articles shed light on the association between obesity and the development of newly diagnosed prostate cancers following primary therapy and outcomes.

Body Mass Index and Risk of Prostate Cancer In U.S. Health Professionals

Giovannucci E, Rimm EB, Liu Y, et al.

J Natl Cancer Inst. 2003;95:1240-1244.

In order to determine the effect of increased body mass index (BMI) on prostate cancer development, the authors examined a longitudinal cohort of men enrolled in the Health Professionals Follow-up Study. This is an ongoing prospective study in the United States of over 51,000 predominantly white, male professionals, ages 40 to 75 years, who were enrolled in 1986. Questionnaires were obtained with relevant clinical information, as well as lifestyle and medical history, at baseline and every 2 years thereafter. Food frequency questionnaires were obtained at baseline and every 4 years thereafter. The questionnaire from 1990 asked whether the patient's father and/or brothers had been diagnosed with prostate cancer. Prostate cancer diagnoses were documented on the follow-up questionnaires and confirmed by exam-

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ination of the medical records. Height and weight were assessed at study enrollment and at 2-year intervals thereafter. Data were available from more than 47,000 of the 51,000 men (some men were excluded because of inadequate follow-up data).

The authors examined the risk over time of being diagnosed with prostate cancer as a function of the baseline BMI obtained upon study enrollment. The advantage of the prospectively collected data, in particular data from the food frequency questionnaires, is that many factors believed to affect prostate cancer risk, such as physical inactivity and high-fat diet, could be adjusted for. Therefore, the analysis of BMI as a predictor for prostate cancer was mutually adjusted for age, year of study, height, smoking, history of diabetes, race, physical activity level, and total caloric intake (including dietary intake of beef, pork, lamb, processed meat, fish, tomato sauce, α-linolenic acid, and calcium).

One study found that as body mass index (BMI) increased, the risk of being diagnosed with prostate cancer decreased in some men. However, for prostate cancer occurring in older men, the higher BMI values offered less protective benefit.

The authors found that as BMI increased, the risk of being diagnosed with prostate cancer significantly decreased. However, this was only true for men < age 60 years or those with a family history of prostate cancer. Men < age 60 years with a BMI ≥ 27.5 kg/m^2 were approximately half as likely to be diagnosed with prostate cancer as men with lower BMI values. The protective effect of increased BMI among men with a family history of prostate cancer was less pronounced, although still significant, for men with a BMI ≥ 25 kg/m.^{2} These men have approximately 25% less risk of being diagnosed with prostate cancer as men with lower BMI values. Higher BMI values were only protective for organ-confined disease and not advanced (extraprostatic) disease. Similar associations were observed when the authors examined waist circumference and BMI at age 21 years.

The authors concluded that perhaps tumors in younger men or those with a family history of prostate cancer are more strongly driven by androgens and that the decreased androgenic activity among men with higher BMI values may be protective. On the other hand, sporadic prostate cancer or prostate cancer occurring in older men may be less dependent upon androgens, and thus higher BMI values would provide no protective benefit.

Impact of Obesity on Biochemical Control After Radical Prostatectomy for Clinically Localized Prostate Cancer: A Report by the Shared Equal Access Regional Cancer Hospital Database Study Group

Freedland SJ, Aronson WJ, Kane CJ, et al.

J Clin Oncol. 2004;22:446-453.

Whereas the previous study examined all men, this study examined only men diagnosed with prostate cancer to determine whether those who are obese have more aggressive disease. To accomplish this, the authors used a large multicenter, multi-ethnic database of men undergoing radical prostatectomy at 5 equal access medical centers, the Shared Equal Access Regional Cancer Hospital (SEARCH) Database.

The authors examined data from 1106 men undergoing radical prostatectomy between 1988 and 2002. They found that obesity in these patients more than doubled in the last 14 years. Black men were significantly more likely to be obese than white men. Obese men also were younger, were more likely to be treated in recent years, and had higher-grade tumors.

The researchers used multivariate analysis adjusting for clinical features of biopsy Gleason score, preoperative serum prostate-specific antigen (PSA) level, age, and year of surgery to determine whether increased BMI was predictive of adverse pathologic features at the time of surgery or the time of biochemical recurrence after surgery. Men with a BMI ≥ 35 kg/m^2 had a 66% increased risk of a positive surgical margin (P = .09). Obesity was not associated with other adverse pathologic features. Therefore, in the absence of other signs of advanced disease, the authors concluded that the higher positive margin rate may have been due to iatrogenic positive margins resulting from the technical difficulty of operating on very obese men.

The higher incidence of obesity among black men may correlate with their increased morbidity and mortality rates from prostate cancer.

On multivariate analysis, a BMI ≥ 35 kg/m^2 was associated with a 2.09-fold (95% CI, 1.30–3.37, P = .002) increased risk of biochemical recurrence. Even after adjusting for the higher incidence of positive surgical margins, a BMI ≥ 35 kg/m^2 was associated with a significantly increased risk of biochemical recurrence (P = .012). On univariate analysis, black men had a higher recurrence rate, although after multivariate adjustment for PSA level and obesity, race was no longer a significant predictor of PSA recurrence.

The authors concluded that because of alterations in

serum hormones, obesity may be associated with a biologically more aggressive form of prostate cancer. Moreover, the authors felt that the higher incidence of obesity among black men may underscore some of the increased morbidity and mortality rates from prostate cancer among black men.

Pathologic Variables and Recurrence Rates as Related to Obesity and Race in Men with Prostate Cancer Undergoing Radical Prostatectomy

Amling CL, Riffenburgh RH, Sun L, et al.

J Clin Oncol. 2004;22:439-445.

This study, published in the same issue, looked at PSA recurrence patterns among obese men after radical prostatectomy. The authors utilized a large multicenter, multiethnic database, similar to the one used in the previous study, of men undergoing radical prostatectomy at 9 active military medical centers, the Center for Prostate Disease Research Database.

Patients were divided into obese (BMI ≥ 30 kg/m^2) and nonobese (BMI < 30 kg/m^2) groups. Consistent with previous studies, the authors found a higher prevalence of obesity among black men. Obese men had higher PSA values and higher-grade tumors than nonobese men. In addition, obese men were more likely to have a positive surgical margin.

On univariate analysis, obese men were significantly more likely to have a PSA recurrence (HR 1.20, 95% CI, 1.02 – 1.42, P = .028). However, after multivariate adjustment, obesity was no longer a significant independent predictor of PSA recurrence. Black men were associated with a higher risk for recurrence in both univariate (P < .002) and multivariate analysis (P = .021).

Similar to the previous study, the authors concluded that because of alterations in serum hormone concentrations, obesity could be associated with a biologically more aggressive form of prostate cancer. The authors also felt higher incidence of obesity among black men may explain some of the increased burden of prostate cancer among black men.

In the previous study, obesity, and not race, predicted outcome in the final multivariate analysis, whereas in this study the opposite results were found. However, this most likely represents a statistical difference between the studies in the choice of different BMI cut-points than true differences in results.

In examining all 3 studies, one must ask, "How can obesity be protective on the one hand and yet be associated with aggressive disease on the other?" Although seemingly contradictory, there is a logical explanation. Consider the following hypothetical cohort of 200 men, 100 of whom are obese and 100 nonobese (Table 1).

On average, 1 out of 6 men will develop prostate cancer (the lifetime risk is approximately 1:6) or about 16 out of 100 men. Approximately 3 of the 16, or 19%, will have advanced disease (extraprostatic) at the time of surgery. Approximately 13 of the 16 men will have organ-confined disease. However, among obese men, if the incidence of all prostate cancer is reduced by 50% (prostate cancer risk was reduced by around 50% in the study by Giovannucci and colleagues among men < age 60 years with an increased BMI), then only 8 men will develop the disease. However, there was no protection for advanced disease, which suggests that the same 3 patients would still develop advanced disease regardless of obesity. Thus, if 3 of 8 have advanced disease, 5 of the 8 must have organ-confined disease. If we now examine only men with prostate cancer, the obese men will be twice as likely to have advanced disease as the nonobese men (3/8 or 38% vs 3/16 or 19%, as shown in Table 1).

In conclusion, the exact relationship between obesity and prostate cancer is still being determined. However, the observations that obesity may be protective and yet at the same time result in more aggressive disease are not mutually exclusive. It is hoped that longer follow-up among all these cohorts will shed more light on the association among obesity, prostate cancer development, and disease progression. ■

Table 1
Effect of Obesity on Prostate Cancer Development and Risk of Advanced Disease in a Hypothetical Cohort

	Nonobese	Obese	Ratio of Nonobese to Obese
Original cohort	100	100	1:1
No. patients diagnosed with prostate cancer	16	8	2:1
No. patients diagnosed with organ-confined prostate cancer	13	5	2.6:1
No. patients diagnosed with advanced prostate cancer	3	3	1:1
Percent of prostate cancer patients with advanced disease	3/16 or 19%	3/8 or 38%	1:2

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