Men with prostate cancer may be at increased risk for metabolic syndrome, cardiovascular disease, and diabetes from androgen deprivation therapy (ADT). This article reviews current literature related to potential adverse effects of using ADT for localized prostate cancer. The use of gonadotropin-releasing hormone agonist therapy for prostate cancer in the early 1990s compared to the late 1990s is addressed. Oncology nurses play an important role in educating men about strategies for preventing and reducing side effects of cancer treatment. Therefore, having knowledge regarding the impact of hormone therapy on men's health will be important to prostate cancer survivors.

At a Glance

- Localized prostate cancer increasingly is managed with androgen deprivation therapy.
- Patients who receive hormone therapy for prostate cancer may have an increased risk of developing metabolic syndrome, cardiovascular disease, and diabetes early in the treatment period.
- Educating men about potential adverse effects of using hormone therapy for prostate cancer is vital.

Gonadotropin-Releasing Hormone Agonist Therapy

Approximately 33% of prostate cancer survivors in the United States currently receive a GnRH agonist (Smith, 2007). Not long ago, this type of ADT was used mainly for metastatic disease (Smith). More recently, GnRH agonist therapy has become part of a management plan for many men with localized prostate cancer (Cooperberg et al., 2003).

A population-based study examined the use of a GnRH agonist in more than 100,000 older adult men with prostate cancer during the 1990s using statistics from the SEER Medicare database (Shahinian et al., 2005). Men with localized prostate cancer represented 36% of the study population, whereas locally advanced or metastatic disease accounted for 21%. In the study, GnRH agonist therapy was initiated within six months of diagnosis and the mean number of doses received was 11.9. The 30% increase in GnRH agonist use was evident for localized and locally advanced prostate cancer.
Prostate cancer. It applied to all age groups and to all grades and stages of disease, even for a large group of men with unknown-stage disease. The significant increase in use of GnRH agonists was seen in two specific categories: adjuvant therapy with radiation therapy and primary therapy in men age 80 or older with localized prostate cancer and with a low- to moderate-grade tumor. The hormone therapy was used minimally when radical prostatectomy was performed. The potential adverse effects of ADT include the development of metabolic syndrome, changes in body composition, cardiovascular disease (CVD), diabetes, insulin resistance, and dyslipidemias.

Metabolic Syndrome

According to a national survey, the age-adjusted prevalence of metabolic syndrome for the general population in the United States is 27.0% (Ford, Giles, & Mokdad, 2004). A definition of metabolic syndrome is outlined in Table 2. Metabolic syndrome may be associated with the development of CVD and diabetes (Lakka et al., 2002). Patients receiving ADT often develop metabolic syndrome (Braga-Basaria et al., 2006; Eri, Urdal, & Bechensteen, 1995; Keating, O’Malley, & Smith, 2006). Early recognition and treatment of this illness may reduce adverse effects of ADT (NCCN, 2008). Adverse effects of GnRH agonist therapy include increased serum triglycerides, increased abdominal fat, and decreased insulin sensitivity (Smith, 2007). A cross-sectional study evaluated the prevalence of metabolic syndrome in 20 men with prostate cancer undergoing at least 12 months of ADT compared to two groups: 18 same-aged men with prostate cancer who received radiotherapy and/or prostatectomy but not ADT and 20 same-aged healthy controls (Braga-Basaria et al.). Racial differences were minimal among the three groups. The non-ADT group and control group were eugonadal (i.e., normal gonadal function). Results show that 55% of men in the ADT group developed metabolic syndrome compared to 22% and 20% of men in the non-ADT and control groups, respectively. Men in the ADT group had higher (p = 0.001) mean body mass index (BMI), higher (p = 0.002) mean fasting glucose levels, and higher (p = 0.007) waist circumference, compared to the non-ADT and control group. Results suggest that hypogonadism is a risk factor for developing metabolic syndrome.

Changes in Body Composition

Hormone therapy may cause changes in body composition. A study evaluated the effects of one three-month GnRH agonist treatment in 22 men with localized or locally advanced prostate cancer (Smith et al., 2001). Results show that mean fat mass increased by 8.4% (p = 0.008) and lean body mass decreased by 2.6% (p = 0.003). Another prospective study evaluated the use of a GnRH agonist in 40 men with locally advanced prostate cancer (Smith et al., 2002). In the study, GnRH agonist treatment was given every 12 weeks for a total of 48 weeks. Findings show that body weight increased by 2.4% (p = 0.005) and percentage fat body mass increased by 9.4% (p < 0.001). In addition, percentage lean body mass decreased by 2.7% (p < 0.001). The cross-sectional tissue analysis using computed tomography (CT) revealed a significant increase in abdominal subcutaneous fat. Only slight intra-abdominal (i.e., visceral) fat accumulation was observed. Also, CT confirmed a decrease in paraspinal muscle size (Smith et al., 2002). Both aforementioned studies imply that a change in body composition is an early adverse effect of GnRH agonist therapy for prostate cancer. The finding is important even when short-term GnRH agonist treatment is being considered in the clinical setting (Smith, 2007).

Men who are very obese also are more likely to receive ADT. A study by Davies et al. (2008) assessed the effect of BMI on treatment patterns for men with localized prostate cancer using data from a large, prospective, community-based Cancer of the Prostate Strategic Urological Research Endeavor national database. Results show that very obese men (i.e., BMI > 35)
have a 77% greater chance (p < 0.001) of receiving ADT than receiving radical prostatectomy as primary treatment for prostate cancer after adjusting for at-risk variables. In the study, a trend was seen toward using nonsurgical methods of prostate cancer treatment such as ADT for an increasing BMI. However, scientific evidence is lacking in regard to nonsurgical modes being the best overall initial treatment for obese men with prostate cancer (Davies et al.). Men with a BMI greater than 35 may be at increased surgical risk, therefore necessitating a nonsurgical approach for treating prostate cancer.

Cardiovascular Disease and Diabetes

Approximately 80.7 million American adults have at least one type of CVD (see Figure 2). Almost half of those people are age 60 or older (American Heart Association, 2008). An estimated 7% of people living in the United States have diabetes; 30% of those people are undiagnosed (National Institute of Diabetes and Digestive and Kidney Diseases, 2005). A population-based study demonstrated an association between using ADT for localized or locally advanced prostate cancer and an increased risk of diabetes and heart-related disease and death (Keating et al., 2006). Researchers extracted information from the SEER Medicare database for the study, which included 73,196 men with prostate cancer older than 65 who were diagnosed from 1992–1999. The mean observation time was 4.6 years. Thirty-six percent of the men received GnRH agonist treatment and 7% underwent bilateral orchiectomy. The authors used Cox proportional hazard models to assess the effect of GnRH agonist treatment or orchiectomy on time to developing new diabetes or new heart-related events. Adjustments were made for patient and tumor characteristics. In the study, men receiving a GnRH agonist had an increased risk of developing incident diabetes, incident coronary heart disease (CHD), sudden cardiac death, and myocardial infarction compared to men not receiving ADT. The increased risk for incident diabetes and CHD occurred after as little as one to four months of GnRH agonist treatment. In addition, men undergoing orchiectomy had an increased risk (p < 0.001) of incident diabetes compared to men treated with neither orchiectomy nor medicinal ADT. One possible explanation is that a limited number of men in the study received surgical castration.

Insulin Resistance

Smith, Lee, and Nathan (2006) evaluated the effects of short-term GnRH agonist treatment on insulin sensitivity in 25 men with locally advanced or recurrent prostate cancer. Patients in the study had no history of diabetes and were nondiabetic at baseline. Blood tests were completed 12 weeks after initiation of GnRH agonist therapy. Results show a significant increase (p < 0.001) in mean glycosylated hemoglobin levels. Mean levels of fasting plasma insulin increased by 25.9%, which can lead to insulin resistance (p = 0.04) (Smith et al., 2006). Of special interest, mean fasting plasma glucose levels increased only slightly. Study results show that GnRH agonist therapy increases the risk of diabetes in older men. Although 80% of the men in the study were overweight or obese, the percentage is only slightly higher than the prevalence of the same weight problems in U.S. men age 60 or older.

Dyslipidemia

Hormone therapy may alter CVD risk factors. A controlled, double-blind study measured serum lipoproteins in 55 older
adult men with benign prostatic hyperplasia (Eri et al., 1995). Blood samples were drawn before, during, and after the men received either GnRH agonist treatment or placebo. In 26 men receiving GnRH agonist therapy, mean total cholesterol increased by 10.6% (p = 0.003) and triglyceride levels increased by 26.9% (p = 0.05) after 24 weeks compared to baseline. For those subjects, total cholesterol and triglyceride levels returned very close to baseline six months after discontinuation of GnRH agonists.

**Primary Prevention Practices**

Based on NCCN guidelines, if ADT is planned for more than one year then patients should be evaluated by their primary physicians prior to initiating ADT. This is especially important for patients with a history of smoking or diabetes (NCCN, 2008). Modifiable risk factors for CVD include obesity, inactivity, smoking, hypertension, alcohol consumption, diet, dyslipidemia, diabetes, and poor psychosocial well-being. Assisting patients to set personalized, achievable goals for reducing these risk factors is important. Offering strategies in the event of setback provides reassurance to patients (Turner, 2007). For patients who receive ADT, assessments should include regular monitoring of total cholesterol, triglycerides, and glycosylated hemoglobin blood levels. Evaluating baseline signs and symptoms for possible metabolic syndrome, CVD, and diabetes is important as part of the initial prostate cancer workup. Regular monitoring for hypertension, central obesity, and an increasing BMI also is important. Positive outcomes for these tests may result from an overweight individual’s participation in a successful weight-loss program. For diabetics and prediabetics, regular doctor visits, glucose monitoring, and diet counseling are important.

Moderate physical activity can delay or reduce the risk of obesity, hypertension, and diabetes. Education is one key to success. But, changing health behaviors is quite challenging and requires more than education. Nurses are in a unique position to support and assist patients in following through with health-promoting lifestyle changes and behaviors (Rice, 2005). A randomized, controlled study examined the effects of resistance and aerobic exercise in 121 men with prostate cancer receiving radiation therapy (Segal et al., 2007). Some men also received ADT. The resistance group and aerobic group each consisted of 40 men who participated in 24 weeks of supervised exercise, whereas the control group consisted of 41 men. The resistance group and aerobic group each had significant improvement in reducing body fat percentage and increasing aerobic fitness compared to controls. Muscular fitness significantly improved in the resistance group compared to controls. Men with prostate cancer were stratified for duration of ADT (non-ADT versus ADT) and randomly assigned to resistance group, aerobic group, or control group. The authors concluded that exercise is beneficial in men undergoing radiation therapy or ADT for prostate cancer.

Central obesity is excess adipose tissue in the upper body, particularly in the abdominal area, and increases the risk of CVD. It is more significant than generalized obesity for the development of metabolic syndrome (Appel, Jones, & Kennedy-Malone, 2004). Central obesity is assessed by measuring waist circumference and is especially useful for assessing risk of CVD in women and minorities. Table 3 shows how overweight and obesity are identified and the formula for calculating BMI and degrees of health risks. A review of epidemiologic studies found no firm evidence for obesity causing an increased incidence in prostate cancer (Hsing et al., 2007). However, data show that obesity consistently increases the risk of prostate cancer aggressiveness and mortality (Hsing et al., 2007). A longitudinal study of 5,200 adults age 65 or older evaluated the combined influence of waist circumference and BMI on risk of waist circumference and BMI on risk of all-cause mortality (Janssen, Katzmarzyk, & Ross, 2005). Elevated BMI values actually can decrease the risk of mortality, after adjusting for waist circumference risks, because BMI may be a reflection of lean body mass. In addition, elevated waist circumference values can increase the risk of mortality, after adjusting for BMI risks. The study found that, in older adults, exercise, which reduces waist circumference but not necessarily body weight, may significantly improve body composition regardless of BMI levels. BMI may reflect lean body mass for people who have the same waist circumference. Waist circumference may reflect total fat content for people who have the same BMI (Bigaard et al., 2003). A new classification system for evaluating health risks in overweight or obese older adults may be required (Janssen et al.).

A low-fat diet together with moderate weight loss may lower the risk of relapse in breast cancer, one type of hormonally dependent, conventionally treated cancer, according to an interim report from the Women’s Intervention Nutrition Study (Chlebowski et al., 2006). Barnard’s (2007) review of scientific evidence (i.e., studies involving humans and rodents) showed that prostate cancer is associated with physical inactivity together with a high-fat, refined-sugar diet. Barnard proposes that prostate cancer promotion and metastasis may be prevented with a low-fat (i.e., 10%-15% of total energy with a properly balanced omega-6/omega-3 fatty acid ratio), complex carbohydrate (e.g., fruits, vegetables, whole grains) diet along with daily aerobic

| Table 3. Formula (Standard and Metric) for Calculating Body Mass Index (BMI) and Health Risk for Type 2 Diabetes, Hypertension, and Cardiovascular Disease for BMI Values |
|-----------------|----------------------------------|
| **BMI**         | **HEALTH RISK**                  |
| 18.5–24.9       | Very low risk                    |
| 25.0–29.9       | Increased risk (overweight)      |
| 30.0–34.9       | High risk (obese)                |
| 35.0–39.9       | Very high risk (obese)           |
| ≥ 40.0          | Extreme risk (obese)             |

**BMI CALCULATION**

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BMI = \frac{weight\ (lb)}{height\ (in)^2} \times 705 \\
BMI = \frac{weight\ (kg)}{height\ (m)^2}
\]

*Note. Based on information from Sizer & Whitney, 2000.*
exercise. The review suggests that consuming foods such as cold-water fish, walnuts, and dark-green, leafy vegetables may help restore the omega-6/omega-3 fatty acid balance in the average North American diet. This may help reduce the risk of developing prostate cancer.

Implications for Nursing

Oncology nurses must know and understand the adverse effects and potential impact on quality of life of various prostate cancer treatments. Scientific evidence shows that men with prostate cancer who receive ADT may become at increased risk for metabolic syndrome and CVD within months of commencing the treatment. Weaker evidence also indicates some potential for diabetes-related adverse effects during the early hormone ablation period. These research findings do not necessarily apply to patients receiving intermittent or neoadjuvant ADT. More research is required to better understand the short- and long-term effects of using ADT for prostate cancer. Oncology nurses’ close monitoring for signs and symptoms of cancer-related and noncancer-related illness while encouraging prevention strategies with diet and physical activity ultimately will lead to improved patient outcomes.

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