Androgen Deprivation Therapy Affects Multiple Bone Properties

Beyond the well-known association of androgen deprivation therapy (ADT) with an accelerated decline in areal bone mineral density (aBMD), the treatment also affects bone in other ways, according to a cross-sectional study.

“The current study is one of few to date that has also measured additional properties of bone, such as the structure of different types of bone, which contributes to overall bone strength and the risk of fracture,” Jack Dalla Via of Deakin University in Geelong, Australia told Reuters Health by email. “This is important as changes or differences in bone structural properties can markedly alter whole bone strength and fracture risk, independent of any change or difference in bone density.

“Our study showed that, in addition to lower DXA-assessed bone density of the lumbar spine, men treated with ADT had lower bone density and reduced bone strength at bone sites of the forearm and lower leg, with the honeycomb-like trabecular bone, rather than the dense cortical bone, mostly affected by this treatment,” he said. “Clinically, this is important because trabecular bone loss starts earlier in life and deteriorates at a greater rate than cortical bone throughout life, with some evidence that it is also more strongly associated with fracture risk than cortical bone.”

Dalla Via and colleagues studied 192 mostly white men with a mean age of about 70: 70 with prostate cancer (PCa) treated with ADT; 52 with PCa but no ADT, and 70 healthy controls.

On average, ADT-treated men had 7.9% higher body mass in-

MRI Plus Systematic Sampling Ups First-Time Prostate Biopsy Hits

In biopsy-naive men, combining MRI with systematic sampling of the imaged lesions increases detection of clinically significant prostate cancer (PCa), according to California-based researchers.

As Dr. Leonard S. Marks stated, “One must do both MRI-targeted and template-systematic biopsies together to maximally find cancer. Either method alone will miss a fair number of cancers.”

In a June 12 online paper in *JAMA Surgery*, Dr. Marks and colleagues at University of California Los Angeles, report that “the optimal method for use of MRI-guided biopsy is not yet clear.”

To investigate, the researchers studied 300 patients, of whom 248 had MRI-visible lesions and the remaining 52 had negative MRI results.

At the same sitting, those with visible lesions underwent both systematic (12 cores) and targeted biopsy (six cores). There were three procedures: a systematic biopsy, an MRI-lesion biopsy targeted by cognitive fusion and thirdly an MRI-lesion biopsy targeted by software fusion. Those with no MRI-visible lesions underwent a 12-core systematic biopsy.

Combining systematic and targeted biopsy results gave an overall cancer-detection rate (CDR) of 70%. This varied from 47% when using cognitive fusion biopsy alone, to approximately 60% when using systematic biopsy or either fusion method alone.

Systematic sampling in the group with no MRI-visible lesions gave a CDR of 15%.

“Discordance of tumor loca-
Is There a Benefit of Addition of Docetaxel, Abiraterone, Celcoxib, or Zoledronic Acid in Initial Treatments for Patients Older Than 70 Years with Hormone-Sensitive Advanced Prostate Cancer? A Meta-Analysis


Clin Genitourin Cancer 13 May 2019; Epub ahead of print

Results from large randomized controlled trials combining docetaxel, abiraterone, celcoxib, or bisphosphonates with androgen deprivation therapy (ADT) in hormone-sensitive prostate cancer (PCa) have emerged. However, in our knowledge, few data are available in men older than 70 years. Therefore, we undertook a meta-analysis of all published phase III studies.

We performed a PubMed search using the keywords: “hormone sensitive PCa,” “phase III studies,” “docetaxel,” “abiraterone,” “celcoxib,” and “bisphosphonates.” We also screened American Society of Clinical Oncology and European Society for Medical Oncology proceedings. Combination therapies were compared with ADT alone. The efficacy outcomes were overall survival (OS) and progression-free survival (PFS). Hazard ratios (HRs) with their 95% confidence intervals (CIs) were collected from the studies and pooled. A HR of less than 1.00 favored the combination group.

This meta-analysis included eight studies: three assessed docetaxel (CHAARTED, STAMPEDE arm E and C), two others assessed abiraterone (LATITUDE and STAMPEDE arm G); two others assessed celcoxib (STAMPEDE arm D and F), and the last one assessed zoledronic acid alone (STAMPEDE arm B). Our meta-analysis included 2,264 men (86% with metastases). Concerning age, we chose a cutoff of 70 years, corresponding to the available data for each study. The performance index was 0 to 1 for about 90% of patients. Overall, in men >70 years old, the addition of docetaxel statistically improved PFS (HR, 0.51; 95% CI, 0.42-0.61) but not OS (HR, 0.86; 95% CI, 0.69-1.07). The addition of abiraterone to ADT also statistically improved PFS (HR, 0.49; 95% CI, 0.37-0.64) but not OS (HR, 0.85; 95% CI, 0.67-1.08), as well as the addition of celcoxib (HR, 0.67; 95% CI, 0.53-0.85 and HR, 0.95; 95% CI, 0.73-1.25, respectively). The addition of zoledronic acid did not improve PFS or OS (HR, 0.78; 95% CI, 0.61-1.00 and HR, 0.99; 95% CI, 0.71-1.38, respectively).

The addition of docetaxel, abiraterone, or celcoxib to ADT significantly increased PFS in older men with hormone-sensitive advanced prostate cancer. However, the benefit in OS is not statistically significant. Further studies are needed to define the best first-line strategy in this subgroup.

Vitamin D Supplementation and Total Cancer Incidence and Mortality

A Meta-Analysis of Randomized Controlled Trials

Keun N, Lee DH, Greenwood DC, Manson JE, Giovannucci E

Ann Oncol 30: 733-743, 2019

Background: Previous meta-analyses of randomized controlled trials (RCTs) of vitamin D supplementation and total cancer incidence and mortality found inconsistent results, and most included trials that administered generally low doses of vitamin D (≤1100 IU/day). We updated the meta-analysis by incorporating recent RCTs that have tested higher doses of vitamin D supplements.

Results:

For total cancer incidence, 10 trials were included [6,537 cases; three-10 years of follow-up; 54-135 nmol/L of attained levels of circulating 25(OH)D in the intervention group]. The summary RR was 0.98 (95% CI, 0.93-1.03; P=0.42; I 2 = 0%, not a significant difference). The results remained null across subgroups tested, including even when attained 25(OH)D levels exceeded 100 nmol/L (RR, 0.95; 95% CI, 0.83-1.09; P=0.48; I 2 = 26%, not a significant difference). For total cancer mortality, five trials were included [1,591 deaths; three-10 years of follow-up; 54-135 nmol/L of attained levels of circulating 25(OH)D in the intervention group]. The summary RR was 0.87 (95% CI, 0.79-0.96; P=0.005; I 2 = 0%, a significant difference), which was largely attributable to interventions with daily dosing (as opposed to infrequent bolus dosing). No statistically significant heterogeneity was observed by attained levels of circulating 25(OH)D.
ADT Affects Multiple Bone Properties (Continued from page 1)

dex than PCa controls but not healthy controls. They were also more likely to have advanced disease and to have been previously treated with radiotherapy or chemotherapy compared to PCa controls, who were more likely to have had a prostatectomy. There were no other relevant differences between groups.

Assessments included lumbar spine DXA, proximal femur aBMD, pQCT distal (4%) and proximal (66%) tibia radius, cortical and trabecular volumetric BMD (vBMD), bone structure, strength and cortical bone distribution.

As reported online June 9 in the journal Bone, ADT-treated men had 7.2-7.8% lower lumbar spine aBMD than either PCa controls or healthy controls, and they trended toward lower total hip aBMD.

At the distal tibia, total bone area was 6.2-7.3% greater in ADT-treated men than in both controls but total vBMD was 8.4-8.7% lower. Further, the bone strength index (BSI) was 10.8% lower in ADT-treated men relative to healthy controls only.

At the distal radius, ADT-treated men had lower total and trabecular vBMD (10.7-14.8%, P<0.05) and BSI (23.6-27.5%) compared to both controls. No other differences in bone outcomes at the proximal tibia or radius were identified.

Summing up, the authors state, “ADT treatment for PCa was associated with lower BMD and estimated compressive bone strength, particularly at trabecular skeletal sites (lumbar spine, and distal tibia and radius), compared to controls, but there were no consistent differences in cortical bone structure, distribution or bending strength.”

“This study reinforces that it is important to monitor bone density in men treated with ADT for PCa,” Dalla Via said.
Non-Hispanic black (NHB) men experience higher risk of prostate cancer (PCa) than other racial/ethnic groups, and it is possible that socioenvironmental (SE) adversity and resulting stress may contribute to this disparity. Data from the Southern Community Cohort Study were used to evaluate associations between SE adversity and perceived stress in relation to PCa risk, overall and by race/ethnicity and grade. Between 2002 and 2009, 26,741 men completed a questionnaire, from which an eight-item SE adversity composite was created (covering socioeconomic status, residential environment, and social support/buffers). Two items from the Perceived Stress Scale were assessed. With follow-up through 2011, 527 PCa cases were diagnosed. In multivariable models, each one-unit increase in the SE adversity composite was associated with increased PCa risk among non-Hispanic white (NHW) men (HR 1.23; 95% CI 1.02-1.48) and reduced risk among NHB men (HR 0.89; 95% CI 0.82-0.95) (p interaction: 0.001). This pattern held for low-grade, but not high-grade, cancers although power was limited for the latter. Perceived stress variables were associated with increased risk of PCa among NHW men, but not among NHB men. Results do not support the hypothesis that SE adversity may underlay the racial disparity in PCa, over and above that of covariates, including healthcare utilization.

Socioenvironmental Adversity and Risk of Prostate Cancer in Non-Hispanic Black and White Men
Kantor ED, Haneuse S, Valdimarsdottir UA, et al.
Cancer Causes & Control 1 July 2019; Epub

Non-Hispanic black (NHB) men experience higher risk of prostate cancer (PCa) than other racial/ethnic groups, and it is possible that socioenvironmental (SE) adversity and resulting stress may contribute to this disparity. Data from the Southern Community Cohort Study were used to evaluate associations between SE adversity and perceived stress in relation to PCa risk, overall and by race/ethnicity and grade. Between 2002 and 2009, 26,741 men completed a questionnaire, from which an eight-item SE adversity composite was created (covering socioeconomic status, residential environment, and social support/buffers). Two items from the Perceived Stress Scale were assessed. With follow-up through 2011, 527 PCa cases were diagnosed. In multivariable models, each one-unit increase in the SE adversity composite was associated with increased PCa risk among non-Hispanic white (NHW) men (HR 1.23; 95% CI 1.02-1.48) and reduced risk among NHB men (HR 0.89; 95% CI 0.82-0.95) (p interaction: 0.001). This pattern held for low-grade, but not high-grade, cancers although power was limited for the latter. Perceived stress variables were associated with increased risk of PCa among NHW men, but not among NHB men. Results do not support the hypothesis that SE adversity may underlay the racial disparity in PCa, over and above that of covariates, including healthcare utilization.

Prostate Cancer Higher in 9/11 Responders – A Look at Why (Continued from page 1)

she added, “and then as a consequence, it stimulates an inflammatory response in the other organs.”

Commenting on the study, David Y. T. Chen, MD, FACS, director, Urologic Oncology Fellowship Program, Fox Chase Cancer Center, Philadelphia, Pennsylvania, explained that epidemiologic evidence has shown that WTC responders have higher rates of cancer of many types compared to people who were not involved. “The primary belief to explain the epidemiologic evidence for this has been hypothesized to be environmental exposures to toxins/carcinogens that were at elevated levels at the WTC site,” he said, “and this study gives some support to that concept. “The higher incidence of many cancers for WTC first responders would justify applying standard cancer screening recommendations,”

(Continued on page 5)
Four-Year Outcomes from a Prospective Phase II Clinical Trial of Moderately Hypofractionated Proton Therapy for Localized Prostate Cancer


Int J Radiat Oncol Biol Phys 11 June 2019; Epub ahead of print

Moderately hypofractionated radiation therapy (RT) represents an effective treatment for localized prostate cancer (PCa). While large randomized trials have shown the efficacy of photon-based hypofractionated therapy, hypofractionated proton therapy (HFPT) has not been extensively studied. This study was done to determine clinical and patient-reported outcomes for men with PCa treated with HFPT.

Between 2010 and 2017, 184 men were enrolled in a trial of HFPT 70Gy in 28 fractions for low- to intermediate-risk PCa. Acute and late toxicity was evaluated by CTCAEv4.0. Patient-reported outcomes were measured by International Prostate Symptom Score (IPSS), International Index of Erectile Function (IIEF) Questionnaire, and Expanded Prostate Cancer Index Composite (EPIC) scores.

Median follow-up was 49.2 months. Enrolled patients had low-risk [LR] (N=18), favorable intermediate-risk [FIR] (N=78), and unfavorable intermediate-risk [UIR] (N=88) PCa. Four-year biochemical disease-free survival (bDFS) was 93.5% (95% Confidence Interval 89-98%), 94.4% (89-100%), and 93.8% (88-100%) in the overall group and the LR, FIR, and UIR cohorts, respectively (logrank p=0.4).

The incidence of acute grade 2 or higher gastrointestinal (GI) and urologic toxicities was 3.8 and 12.5%, respectively. Four-year incidence of late grade 2 or higher urologic and GI toxicity was 7.6% (4-13%) and 13.6% (9-20%), respectively. One late grade 3 GI toxicity was reported. All late toxicities were transient. Patient-reported IPSS, IIEF, and EPIC scores had no significant long-term changes following HFPT completion.

HFPT is associated with low rates of toxicity and does not appear to negatively impact four-year patient reported urinary and bowel health. Further comparative analyses are warranted to better understand the differences between HFRT using proton beam and photon RT.

Association Between Androgen Deprivation Therapy Use and Diagnosis of Dementia in Men with Prostate Cancer


JAMA Netw Open 2019; 2: e196562

Key Points

Question: Is androgen deprivation therapy (ADT) exposure associated with dementia among elderly patients with prostate cancer (PCa)?

Findings: In this cohort study of 154,089 elderly men with PCa, ADT exposure was associated with subsequent diagnosis of Alzheimer’s disease or dementia in elderly men with PCa.

Meaning: Clinicians must carefully weigh the long-term risks and benefits of exposure to ADT in men with a prolonged life expectancy and stratify men by dementia risk prior to ADT initiation.

Importance: The association between ADT exposure and dementia is uncertain.

Objective: To analyze the association between ADT exposure and diagnosis of Alzheimer’s or dementia during follow-up. Propensity score and instrumental variable approaches were used to minimize measured and unmeasured selection bias. Association by dose of ADT was also examined.

Results: Of the 295,733 men diagnosed with PCa between 1996 and 2003, 154,089 met the study criteria. Of these, 62,330 (mean [SD] age, 76.0 [6.0] years) received ADT within two years of PCa diagnosis, and 91,759 (mean [SD] age, 74.3 [6.0] years) did not receive ADT. Mean (SD) follow-up was 8.3 (4.7) years. Exposure to ADT vs. no ADT exposure was associated with a diagnosis of Alzheimer’s (13.1 vs. 9.4%; difference, 3.7%; 95% Confidence Interval, 3.3-3.9%; P <0.001; hazard ratio [HR], 1.14; [1.10-1.18]) and dementia (21.6 vs. 15.8%; difference, 5.8%; [5.4-6.2%]; P <0.001; HR, 1.20; [1.17-1.24]). For one to four doses of ADT, the HR was 1.19 for Alzheimer’s and 1.19 for dementia. For five to eight doses of ADT, the HR was 1.28 for Alzheimer’s and 1.24 for dementia. For more than eight doses of ADT, the HR was 1.24 for Alzheimer’s and 1.21 for dementia. The number needed to harm was 18 and 10 men for Alzheimer’s and dementia, respectively.

Conclusions and Relevance: Among elderly men with PCa, ADT exposure was associated with subsequent diagnosis of Alzheimer’s disease or dementia over a follow-up period of at least 10 years.
Body Fat Distribution Points to Prostate Cancer Aggressiveness

Body fat distribution may be related to prostate cancer (PCa) aggressiveness. Men with high levels of visceral fat have an increased risk of developing advanced PCAs, while those with increased subcutaneous (SQ) fat in the thigh are more likely to die from the disease, suggests an analysis of prospective data from Iceland.

Barbra A. Dickerman, PhD, Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, and colleagues studied more than 1,800 Icelandic men followed up for up to 13 years after a comprehensive medical exam. While increases in body mass index (BMI) and waist circumference were associated with a significant increased risk of both advanced and fatal PCAs, accumulation of fat in specific areas also influenced risk.

The researchers found that each unit increase in visceral fat was associated with a 31% increased risk of advanced PCAs, while a unit increase in SQ thigh fat increased the risk of fatal PCAs by 37%. Notably, the association between visceral fat and advanced and fatal PCAs was significant only in men with a lower BMI. The findings, which were published in Cancer on June 10, underline the imprecise nature of BMI and waist circumference when examining the relationship between adiposity and disease risk, say the authors.

“Studies of BMI or waist circumference alone may not capture important sub-phenotypes, and this may explain the heterogeneity of previous findings for obesity and PCAs,” they write. Calling for prospective studies of fat distribution and PCAs outcomes, they say that identifying “the adiposity pheno-
types at highest risk of clinically relevant PCAs may help to elucidate the mechanisms linking obesity with aggressive disease and target intervention strategies.”

Dickerman stated the study has a number of strengths, including the complete and reliable data and the long follow-up, however, the participants were exclusively older, white men meaning that the results “may not be generalizable to younger, more diverse groups.”

Nevertheless, the findings highlight that measuring BMI alone may “miss” high-risk patients, and they “open up new directions for future research to investigate how measures of fat distribution can be integrated clinically to inform targeted prevention and treatment strategies.”

Dickerman added that the finding of a stronger association between visceral fat and advanced PCa in men with a lower BMI requires “further investigation.” She said, “It is possible that higher visceral fat may be a marker for an underlying physical activity pattern or hormonal milieu that influences both fat distribution and risk of advanced disease. For example, fat may be preferentially deposited in the visceral depot among leaner men in the presence of a particular hormonal milieu.”

Dickerman continued, “If this hormonal milieu is also a risk factor for advanced PCAs, this may partially explain the results of our analyses stratified by BMI.”

Obesity measures such as BMI and waist circumference have been consistently associated with an increased risk of advanced PCa and a poorer prognosis. However, there is increasing evidence that body fat distribution may be an important prognostic risk factor for PCa outcomes. The authors note that this may reflect differences in metabolic, hormonal, and inflammatory markers between fat locations. For example, visceral fat is associated with proinflammatory cytokines and inversely associated with bioavailable testosterone, while intramuscular fat in the thigh is linked to worse glucose tolerance.

To examine the role of body fat distribution in PCa risk, the researchers studied data from the Age, Gene/Environment Susceptibility-Reykjavik study, wherein a random sample of participants underwent comprehensive medical examinations between 2002 and 2006. Excluding participants with a history of cancer, those without complete computed tomography data, and those with a BMI <18.5 kg/m², the team were left with 1,832 men.

The Icelandic Cancer Registry was then used to identify PCa cases diagnosed up to the end of 2015, with cases categorized as high-grade, advanced, or fatal, based on Gleason grade and stage. The mean age of the men at study entry was approximately 67 and the mean BMI was between 24.5 kg/m² and 29.3 kg/m². The mean percentage body fat lay between 18.8% and 25.1%.

Men with higher visceral fat had, unsurprisingly, a higher BMI and waist circumference than men with less visceral fat. They also had less physical activity during youth and midlife and were less likely to be current smokers. Over the study period, there were 172 PCa diagnoses and 31 PCa-specific deaths. Forty one cases were advanced and 43 were high-grade. The median time to PCa diagnosis and to PCa death was 10.1 and 10.4 years, respectively.

Visceral fat was associated with an increased risk of advanced PCa, at a hazard ratio (HR) of 1.31 per standard deviation (SD) increase, while thigh SQ fat increased the risk of fatal PCa at a HR of 1.37 per SD increase. Interestingly, the strength of the association was modulated by BMI, with the link between visceral fat and advanced and fatal PCa significant among men with BMI <27 kg/m² but not significant for men with a greater BMI. The results for total and percentage fat mass were similar to those for visceral and thigh SQ fat.

The researchers also calculated that each 5 kg/m² increase in BMI increased the risk of both advanced and fatal PCa, at HRs of 1.52 and 1.56, respectively. Compared with men with a healthy BMI, those with BMI ≥30 kg/m² had a significantly increased risk of advanced and fatal PCa.

(Continued on page 8)
P1, “MRI Plus Systematic...”
The optimal approach to evaluating men with an elevated PSA continues to evolve. MRI-guided biopsies can clearly find cancers missed by systematic biopsies and vice-versa. Marks and co-workers conducted an assessment that combined systematic biopsies with cognitive fusion and software fusion-guided MRI. They found that each misses some significant cancers, defined as grade group 2 or higher. They recommend either form of MRI-guided biopsies plus systematic biopsies because it appeared that each method detected prostate cancer (PCa) in different locations.

Results of other studies suggest MRI could substitute for systematic biopsies and reduce the likelihood of finding non-life threatening PCa. This study suggests a significant number of dangerous cancers would still be missed. Authors did not report the number of low-risk cancers detected by each method.

The Bottom Line: The optimal approach to first-time prostate biopsy continues to evolve with mounting evidence that MRI guidance is necessary, but support for performing systematic biopsies is less certain.

P2, “Vitamin D...” Vitamin D has become one of the most recognized supplements heralded for its potential health benefits and it is one of the few with results supported by properly designed studies. Now, Krum and co-workers conducted a meta-analysis of randomized studies that showed a statistically significant reduction in overall PCa mortality at ten years, but no statistically significant reduction in PCa incidence. There are many questions to consider, such as: at what age Vitamin D therapy must be started; whether the benefit is due to a specific type of Vitamin D; why it reduces the risk of mortality but not the incidence of developing PCa; and why adequate dietary Vitamin D is not beneficial. Nevertheless, Vitamin D may be of value for those seeking to improve their health.

The Bottom Line: Daily ingestion of Vitamin D appears to reduce an individual’s risk of dying from PCa.

P5, “Four-Year Outcomes...”
The relative value of proton beam radiotherapy (RT) vs. photon RT remains unclear due to a lack of randomized comparisons. Attempts to compare cohort studies will always be problematic. Ongoing studies with hypofractionated (HF) proton RT show acceptable short-term outcomes; however studies reporting long-term outcomes are not yet available. Now, we have a study of HF proton beam RT reported by Grewal and co-workers with four-year median follow-up. The research team reported biochemical disease-free survival (bDFS) for a small sample of men with low-risk, favorable-intermediate-risk and unfavorable-intermediate-risk disease. It is important to review the estimated and range of outcomes carefully because the sample size is small and the length of follow-up is short. That being said, there is concern about using this approach, even for the low- and favorable-risk-intermediate cases because the ranges of bDFS could be as high as 11% for low-risk and low intermediate-risk disease. In men with little risk of dying, there is a concern that many more men would fail treatment because the risk of that outcome could be underestimated. More importantly, bDFS is not a valid predictor of OS. In addition, the 13% rate of late grade 2 or higher genitourinary (GU) side effects is a concern in men with a very low risk of disease progression if left untreated. As discussed so often in this column, these flaws in study design make it nearly impossible to determine the relative value of this treatment compared to others.

The Bottom Line: Short-term outcomes from HF proton beam RT are a concern and patients should only be offered this option via an investigation study.

P5, “Association Between...”
Although ADT has bestowed significant benefits for the majority of advanced PCa cases, it is not without risks. Now, a retrospective analysis by Jayadevapp, et al. adds the possibility that ADT affects the risk of dementia and Alzheimer’s disease. Researchers analyzed data from the SEER database and compared the risk of men developing these neurological diseases based on the number of doses of ADT they received. The study cohort was very large, and included men treated between 1996 and 2003 with at least ten years of follow-up. They found that treatment with one to four doses increased the risk of each disease with risk increasing with high numbers of doses. The risk affected about one out of 18 men. First, use caution when drawing conclusions given the likelihood for biased results from this retrospective, non-randomized assessment. Second, as with all cancer therapies, there are known trade-offs between risks and benefits. For men with advanced PCa where average survival is five years, adverse consequences may be of lesser concern. Nevertheless, it may be appropriate to discuss this while presenting other ADT risks to a PCa patient. For now, it may be premature to conclude that this risk is real.

The Bottom Line: More data are required that demonstrate an increased risk of dementia and Alzheimer’s disease in men receiving ADT.
risk of advanced PCa, at a HR of 2.54, and an increased risk of fatal cancer, at a HR of 2.59. Similarly, each SD increase in waist circumference was associated with an increased risk of advanced and fatal PCa, at HRs of 1.40 and 1.45, respectively.

In an accompanying editorial, Celina H. Shirazipour, PhD, and Stephen J. Freedland, MD, from Cedars-Sinai Medical Center, Los Angeles, argue that looking at the current results in the context of the evidence around diet and exercise offers “new opportunities” for researchers and clinicians alike.

“First, researchers could benefit from including measures that assess visceral fat as outcomes in interventions, whereas clinicians would benefit from collecting knowledge of fat location in addition to the total weight.” Shirazipour and Freedland write, “Although a direct association was not made, through knowledge of the importance of diet and physical activity in targeting fat, interventions should prioritize targeting these lifestyle factors during youth or emerging adulthood in order to decrease the risk of PCa.”

Responding to these comments, Dickerman said that the study’s findings “alone do not provide evidence for a specific intervention for PCa risk reduction. However, they can, as the editorial suggests, help to generate hypotheses for future research on specific interventions”

More broadly, she agreed with the researchers that the findings show that “we can’t just focus on a BMI number; that we need to look more deeply,” which is “very important” when talking to patients in the clinic. The current findings at least “add to the knowledge that clinicians can use.”

Medscape Medical News
13 June 2019

MRI Plus Systematic Sampling (Continued from page 1)

... Dr. Lee added that the research addresses “an important issue about the role of traditional systematic prostate biopsy in the era of MRI-guided sampling. This study affirms the importance of MRI-guided biopsy in the detection of clinically significant PCa, but also demonstrates additional value in the concomitant use of systematic biopsy.”

Medscape
21 Jun 2019

Vitamin D
(Continued from page 2)

... Conclusions: In an updated meta-analysis of RCTs, vitamin D supplementation significantly reduced total cancer mortality but did not reduce total cancer incidence.
Between the Sheets...
August 2019

This column provides the platform for experts in the field to help men and women by providing answers to questions about sexual health and intimacy challenges that can result from prostate cancer treatment.

This column was compiled with the help of Dr. Anne Katz, Certified Sexuality Counselor and Clinical Nurse Specialist at CancerCare Manitoba. She has educated thousands of healthcare providers and cancer survivors about cancer, sexuality and survivorship. She is the editor of the Oncology Nursing Forum, an avid blogger for ASCO Connections, and the author of 13 books on the topics of illness, sexuality and cancer survivorship. (www.drannekatz.com)

QUESTION FROM PROSTATE CANCER SURVIVOR:
Since going on hormone therapy I have gained a lot of weight. I don’t know what to do about this – I have tried dieting and the weight won’t budge. I have had to buy new clothes and I can’t wear polo shirts anymore because of my bulging stomach; I look terrible in everything. I know that men aren’t supposed to bother about this, but I do and it’s costing me a lot of money!

RESPONSE FROM DR. ANNE KATZ:
Weight gain is one of the more distressing side effects of androgen deprivation therapy (what is commonly called “hormone therapy”). The weight gain tends to be around the abdominal area and is often called the “spare tire.” It is VERY bothersome for many men and, yes, costly too when you have to “size up” and buy a new wardrobe. And men DO care about how they look, so you are allowed to be frustrated by this.

Unfortunately most diets don’t seem to work to shift this weight gain but it is VERY important that you eat a “heart healthy” diet to prevent the development or worsening of diabetes and/or cardiovascular disease. The CDC has resources to inform and educate about this. They can be found on their website at https://www.cdc.gov/obesity/resources/factsheets.html.

The other important thing that you MUST do while on this treatment is to get both resistance AND aerobic exercise. Resistance exercise can be done with free weights or resistance bands, or even large tin cans! Aerobic exercise needs to be weight bearing, like walking at a moderate to fast pace. You should also be taking calcium and Vitamin D supplements as prescribed by your health care provider(s).

And, of course, this can affect your sexual relationship. Some men feel embarrassed about undressing in front of their partner and additional weight around your ‘middle’ may make intercourse challenging. You and your partner may have to think about different positions for intercourse as well. Coupled with the loss of upper body strength, intercourse in the man on top position may be more tiring for you. It is VERY important to talk to your sexual partner about this as they may not know how this weight gain is affecting you and may blame themselves if you start to withdraw emotionally or sexually.

If you are able to go off the medication, even for a “drug holiday,” you may find that some of the weight does come off with adherence to a heart healthy diet.

Watch Dr. Katz’ presentation on sexual health and intimacy from the Prostate Cancer Pathways for Patients and Caregivers event recorded at Englewood Health in Englewood, NJ on September 29, 2018. https://www.youtube.com/watch?v=A2ZdDHw2WGY&t=8542s.

Read previous issues of Between the Sheets at www.ustoo.org/BTS.

Do you have a question about sexual health or intimacy? If so, we invite you to send it to Us TOO. We’ll select questions to feature in future Between the Sheets columns.

Please email your question to: ustoobts@ustoo.org

Or mail your letter to:
Us TOO International
Between the Sheets
2720 S. River Road, Suite 112
Des Plaines, IL 0018
Progress on Prostate Cancer Research

Advancements in prostate cancer research provide hope for finding a cure and lead to the discovery of new treatments to minimize the impact of a man’s prostate cancer and maximize his quality of life. This regular Hot SHEET supplement includes some of the latest research from the Prostate Cancer Foundation (www.pcf.org).

The PCF is the world’s leading philanthropic organization funding and accelerating prostate cancer research. Founded in 1993, the PCF has raised more than $745 million and provided funding to more than 2,000 research programs at nearly 200 cancer centers and universities.

Studying the Effects of ADT on Brain Function

Androgen deprivation therapy (ADT) is a primary treatment for prostate cancer, and acts by blocking the production or action of testosterone and other male hormones that activate the androgen receptor (AR). Studies have suggested that ADT may affect cognition and has been associated with the development of Alzheimer’s disease and dementia. (See page 5 of this month’s Hot SHEET for an example of such a study.) However, biological evidence to support this effect has not yet been demonstrated. Moreover, whether and how clinicians should act upon this knowledge when selecting treatments for patients is unclear. Patients with prostate cancer are surviving for a longer time on ADT and more potent AR-targeted therapy (i.e. abiraterone, enzalutamide, and apalutamide). Thus, it is critical to understand if and how these treatments contribute to cognitive decline.

Overall, cognition in men with prostate cancer can be affected by three categories of factors:

1. Genetic effects: Activity of the AR can be affected by differences in the gene that gives instructions for cells to make the AR protein; a larger, less active AR protein is associated with a higher risk of cognitive impairment when patients are treated with ADT
2. Patient effects, such as age and other co-occurring illnesses; androgen levels in the brain decrease with age
3. Drug effects: For patients on ADT, the ability of the drug to penetrate the blood-brain barrier and how effectively the drug targets the AR in the brain

How Does Testosterone Work in the Brain?

Androgen receptors (AR) are found in the brain and perform several critical functions. AR and testosterone play a role in memory, emotional function, and cognitive function in general. Low testosterone levels are known to impair these functions. Testosterone has also been found to protect brain cells from death. Thus, the brain may be an unintended target of ADT and AR-targeted therapy.

Two PCF-funded researchers aim to determine the contribution of each of these factors to cognitive impairment in prostate cancer patients being treated with ADT or other AR-targeted therapies. Dr. Alicia Morgans is an Associate Professor of Medicine at the Northwestern University Feinberg School of Medicine, and Dr. Charles Ryan is a Professor of Medicine and B.J. Kennedy Chair in Clinical Medical Oncology at the University of Minnesota. Precision survivorship is a field of medical research and clinical practice that aims to identify vulnerable populations at increased risk for adverse outcomes from cancer treatments, understand the biology and genetic factors underlying these effects, and use this information to select personalized treatments that will maximize a patient’s long-term quality of life. Drs. Morgans and Ryan’s precision survivorship studies aim to identify patients who are at risk of cognitive impairment with AR-targeted therapies, and identify treatment strategies to prevent or reverse cognitive decline without compromising survival.

One such study, called ARACOG, is a randomized phase 2 trial to compare cognitive effects in men with advanced prostate cancer undergoing treatment with ADT + enzalutamide vs. darolutamide. Enzalutamide has been found to cross the blood-brain barrier and penetrate the brain, while darolutamide (a new drug that is up for FDA approval) appears unable to cross the blood-brain barrier. These differences have led Drs. Morgans and Ryan to hypothesize that enzalutamide may cause cognitive impairment while darolutamide will not. In ARACOG, men with castration-resistant prostate cancer who have not received prior second-generation AR-targeted therapy will be randomized to receive enzalutamide or darolutamide (+ ADT). Patients’ cognitive function and brain activation (using functional MRI) will be evaluated at baseline and over the course of treatment, up to one year.

This study will contribute to the body of knowledge about treatments for advanced prostate cancer by defining the proportion of prostate cancer patients who have baseline cognitive impairment, characterizing the biology of the effects of low testosterone and AR inhibition in the brain, and comparing the cognitive effects of two different therapies. Importantly, results will help to identify high-risk patients who can be selectively enrolled in future intervention studies.

Talk to your doctor about whether enrolling in a clinical trial may be right for you.

For more information visit www.pcf.org, email info@pcf.org, or call 1-800-757-2873.