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Hot SHEET

Us TOO INTERNATIONAL Prostate Cancer Education and Support Network

More Benefit with Taxane for Aggressive Metastatic Prostate Cancer

Higher Clinical Benefit Rate with Front-Line Cabazitaxel vs. Androgen Receptor Inhibitor

Men with poor-prognosis metastatic castration-resistant prostate cancer (mCRPC) had better outcomes with cabazitaxel as initial therapy instead of an androgen-receptor-pathway inhibitor (ARPI), a phase II randomized trial showed. "First-line taxane therapy led to a clinical benefit rate (CBR, response plus stable disease) of 80 vs. 62% for men treated with an ARPI – either enzalutamide or abiraterone. Men treated with cabazitaxel

lived more than twice as long, although the difference did not reach statistical significance because of a small patient population. Patients treated with cabazitaxel had higher rates of grade ≥ 3 neutropenia, diarrhea, and infection," reported Kim N. Chi, MD, of BC Cancer in Vancouver, and colleagues, in *Annals of Oncology*. "Cabazitaxel was associated with a modestly higher CBR compared to ARPI," the authors concluded. "However,

both treatments should remain important options for men with ARPI-naïve mCRPC. CtDNA (circulating tumor DNA) abundance was prognostic, independent of clinical features, and holds promise as a stratification biomarker. "Disease progression despite castrate testosterone levels defines mCRPC. Clinical trials of first-line treatment with ARPIs led to median overall

(Continued on page 5)

Prostate Radiation Therapy Tied to Improved Survival in Newly Diagnosed Metastatic Hormone-Sensitive Prostate Cancer

Radiation therapy (RT) directed at the primary prostate tumor in patients with newly diagnosed metastatic hormone-sensitive prostate cancer (mHSPC) is associated with a statistically and clinically significant improvement in overall survival (OS), according to a recent study.

Scott C. Morgan, MD, of The Ottawa Hospital Cancer Centre in Ottawa, Canada, and colleagues studied a cohort of 410 men with newly diagnosed mHSPC referred to a comprehensive cancer center from 2005 to 2015. Of these, 128 received prostate RT and 282 did not. All initially received androgen deprivation therapy (ADT). Median follow-up duration was 61 months.

"The median OS was 47.4 months for the prostate RT group compared with 26.3 months for patients who did not receive prostate RT. On multivariate analysis, prostate RT was significantly associated with a 31% decreased risk of death compared with no prostate RT," the investigators reported online in *Prostate Cancer and Prostatic Diseases*.

"In addition, among patients who received prostate RT, OS improved along with increases in the biologically effective RT dose. Each 10 Gy increase was significantly associated with a 13% decreased risk of death," according to the investigators.

"To our knowledge, this cohort represents the largest single-institution experience with primary tumor-directed RT in mHSPC to date," Dr. Morgan's team wrote. "Receipt of

(Continued on page 8)

Healthy Lifestyle May Offset Genetic Risk in Prostate Cancer

Adhering to a healthy lifestyle may offset the heightened risk of lethal prostate cancer (PCa) in men with adverse genetic risk factors, according to results of a large U.S. study.

"In men at the highest risk of PCa death, having the highest healthy lifestyle scores cut the risk of fatal disease in half," said study author Anna Plym, PhD, of Brigham and Women's Hospital and Harvard School of Public Health, both in Boston. She presented these findings at the American Association for Cancer Research (AACR) 2021 Annual Meeting.

Plym noted that genetic factors account for about 58% of variability in PCa risk, with common single-nucleotide polymorphisms (SNPs) accounting for a large proportion of PCa susceptibility.

"A recent study showed that a polygenic risk score (PRS) derived by combining information from 269 SNPs was highly predictive of PCa," Plym said. There was a 10-fold gradient in disease risk between the lowest and highest genetic risk deciles, and the pattern was consistent across ethnic groups. "In addition," Plym noted, "previous studies have suggested that a healthy lifestyle reduces lethal PCa risk."

What remains unclear is whether the risk for both PCa development and the risk of progression to lethal disease can be offset by adherence to a healthy lifestyle.

To investigate, Plym and colleagues used the 269-SNP PRS to quantify the genetic risk of PCa in 10,443 men enrolled in the Health Profes-

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Transperineal Prostate Biopsy Improves the Detection of Clinically Significant Prostate Cancer Among Men on Active Surveillance

Meyer AR, Mamawala M, Winoker JS, landis P, Epstein JI, et al.

J Urol 205: 1069-1074, 2021

Purpose: Transperineal prostate biopsy offers improved sampling of the anterior prostate compared to the transrectal approach. The objective of this study was to determine if transperineal prostate biopsy is associated with an increased incidence of cancer upgrading among men on active surveillance (AS) for very low- or low-risk prostate cancer (PCa).

Materials and Methods: Our AS registry was queried to identify men who underwent a surveillance biopsy following the introduction of transperineal prostate biopsy. Patients were dichotomized by the type of biopsy performed. The baseline characteristics and rates of cancer upgrading were compared between groups.

Results: Between November 2017 and June 2020, 790 men with very low- or low-risk PCa underwent a surveillance biopsy. In total, 59 of 279 men (21.2%) in the transperineal prostate biopsy group were upgraded to grade group ≥ 2 as compared to 75 of 511 (14.7%) in the transrectal biopsy group ($p=0.01$, a statistically significant difference). Among patients who were upgraded to grade group ≥ 2 , 26 of 59 (44%) had grade group ≥ 2 detected in the anterior/transition zone with transperineal prostate biopsy compared to 14 of 75 (18.7%) with transrectal biopsy ($p=0.01$, a statistically significant difference). Additionally, 17 of 279 men (6.1%) who underwent transperineal prostate biopsy

were upgraded to grade group ≥ 3 vs. 17 of 511 (3.3%) who underwent transrectal biopsy ($p=0.05$). After adjusting for age, prostate specific antigen density, use of magnetic resonance imaging, and number of prior transrectal biopsies, transperineal prostate biopsy was significantly associated with upgrading to grade group ≥ 2 (OR 1.49, 95% CI 1.11-2.19, $p=0.01$).

Conclusions: Among men on active surveillance for very low- or low-risk PCa, transperineal prostate biopsy was associated with an increased likelihood of upgrading to clinically significant PCa. This is likely due to improved sampling of the anterior prostate with the transperineal approach.

Impact of a Genomic Test on Treatment Decision in a Predominantly African American Population with Favorable-Risk Prostate Cancer, a Randomized Trial

Murphy AB, Abern MR, Liu L, et al.

J Clin Oncol, E-Pub 09 April 2021

Purpose: The Genomic Prostate Score (GPS), performed on biopsy tissue, predicts adverse outcomes in prostate cancer (PCa) and has shown promise for improving patient selection for active surveillance (AS). However, its impact on treatment choice in high-risk populations of African Americans is largely unknown and, in general, the effect of GPS on this difficult decision has not been evaluated in randomized trials.

Methods: Two hundred men with very low- to low-intermediate-risk PCa from 3 Chicago hospitals (70% Black, 16% college graduates) were randomly assigned to diagnosis to standard counseling, with or without a 12-gene

GPS assay. The primary end point was treatment choice at a second postdiagnosis visit. The proportion of men choosing AS was compared, and multivariable modeling was used to estimate effects of various factors on AS acceptance.

Results: AS acceptance was high overall, although marginally lower in the intervention group (77 vs. 88%; $P = 0.067$), and lower still when men with inadequate specimens were excluded ($P = 0.029$). Men with lower health literacy who received a GPS were seven-fold less likely to choose AS compared with controls, whereas no difference was seen in men with higher health literacy ($P_{\text{interaction}} = 0.022$). Among

men with low-intermediate-risk, 69% had GPS values consistent with unfavorable intermediate- or high-risk cancer. AS choice was also independently associated with a family history of PCa and having health insurance.

Conclusion: In contrast to other studies, the net effect of the GPS was to move patients away from AS, primarily among men with low health literacy. These findings have implications for our understanding of how prognostic molecular assays that generate probabilities of poor outcome can affect treatment decisions in diverse clinical populations.

Doc Moyad's What Works & What is Worthless Column – Also Known as “No Bogus Science” Column

“The Chicken, Egg, or Lifestyle?!”

Mark A. Moyad, MD, MPH, University of Michigan Medical Center, Department of Urology

Editor's Note: Us TOO invites certain physicians and others to provide information and commentary for the *Hot SHEET* to enrich its content to empower the reader. This column contains the opinions and thoughts of its author and are not necessarily those of Us TOO International.

You know the jaded introspective philosophical question... was it the “chicken or the egg” that came first? We are missing the true meaning of its implication in the Moyad world. There are 1000s upon 1000s of dietary studies released each year and I watch many folks utilize a select number of them to make an argument as to why a certain beverage or food is 100% wonderful or evil. But, what gets missed in the arguments of primarily observational studies is that it is nearly impossible to pin the blame, or even the good, on one food product. It could, in reality, be the comprehensive (“sum of what you do and that occurs to you”) lifestyle issues, or benefits, or risks that could be the real answer to the dilemma and this, my friends and foes, never seems to garner the attention it deserves. So we are going to give it some attention here.

This brings us to one of the largest (over 500,000 people) comprehensive observational studies ever in the U.S. that recently found increasing your consumption of whole eggs could increase the risk of dying younger from all causes. Yikes, that does not get me “eggcited” to eat eggs, which I do like very much, once in a while - not often, but once in a while (phew - got out of that controversy). Basically, the consumption of whole eggs and dietary cholesterol in the study were “associated” with a higher risk of dying earlier from all-causes, including cardiovascular disease (CVD) and cancer. Notice how the authors use the words “associated” because they

cannot prove cause and effect, but an association. When you read through the entire study, which I did because I have no social life, then you notice something in the group of people consuming the highest amounts of eggs. As a group, subjects were more likely to be in poor health, less likely to use common preventive medicines, consumed the least amount of fiber, less nuts, less beans, less fruits, less veggies, less whole grains (emphasis on “less”), had the highest amount of red meat consumption, lowest scores of a comprehensive eating index questionnaire, more likely to currently smoke and be of a higher body mass index (BMI), blah, blah, blah. Lifestyle changes rely on MOMENTUM, so the more and more healthy behaviors you incorporate, then the more momentum you have to keep going and adding more and more healthy changes. The person who quits smoking begins to think about diet, then exercise, then blood cholesterol, blood pressure, sugar, etc. Thus, I believe the researchers from this great study also found those consuming egg white/substitutes had a lower risk of dying from most of these same diseases. However, remember, the antithesis is true. As you follow less healthy behaviors, it gets easier and easier to add even more unhealthy behaviors to your lifestyle. You smoke or use tobacco, it is then easier to drink too much, exercise even less, pay less attention to diet, sleep more poorly, blah, blah, blah. Statisticians (keep in mind this is also part of my back-

ground, so I am criticizing myself here) love to say in these studies that they corrected or statistically adjusted for all these behaviors, but if you know statistics, then you know there is no way all of these factors can be truly accounted for by a questionnaire because there are unappreciated behaviors that will never be picked up in any study. So, people walk away “pecking” (get it?) or picking solely on the egg when there is a greater lesson here to be learned.

Therapies for Clinically Localized Prostate Cancer: A Comparative Effectiveness Review

Wilt TJ, Ullman KE, Linskens EJ, et al.

J Urol 205: 967-976, 2021

Purpose: We sought to identify new information evaluating clinically localized prostate cancer (PCa) therapies.

Materials and Methods: Bibliographic databases (2013-January 2020), ClinicalTrials.gov and systematic reviews were searched for controlled studies of treatments for clinically localized PCa with duration ≥ 5 years for mortality and metastases, and ≥ 1 year for harms.

Results: We identified 67 eligible references. Among men with clinically, rather than PSA-detected localized PCa, watchful waiting (WW) may increase mortality and metastases but decrease urinary and erectile dysfunction vs. radical prostatectomy (RP). Comparative mortality effect may vary by tumor risk and age but not by race, health status, comorbidities, or PSA. WW probably results in little to no mortality difference in PSA detected localized PCa vs. RP or external beam radiation ther-

So, what did come first, the chicken, or the egg? Who cares!? First I want to know what was going on in the life or the environment of that chicken, or that egg, that needs to change, so it can potentially live longer and better, and that my friends is very serious - no yoke!

By the way, why did the chicken cross the internet? To get to the other site!

Reference:

1. Zhuang P, Wu F, Mao L, et al. *PLoS Med*; 18: e1003508, 09FEB2021

apy (EBRT) plus androgen deprivation (AD), regardless of tumor risk. Metastases were slightly higher with active monitoring. Harms were greater with RP than WW and mixed between EBRT plus AD vs. WW. 3-dimensional conformal RT (3D-CRT) and AD plus low dose rate brachytherapy provided small mortality reductions vs. 3D-CRT and AD, but little to no difference on metastases. EBRT plus AD vs. EBRT alone may result in small mortality and metastasis reductions in higher-risk disease but may increase sexual harms. Few new data exist on other treatments.

Conclusions: RP reduces mortality vs. WW in clinically detected localized PCa but causes more harms. Effectiveness may be limited to younger men and those with intermediate-risk disease. WW results in little to no mortality difference vs. RP or EBRT plus AD. Few new data exist on other treatments.

Estimated Projection of US Cancer Incidence and Death to 2040

Rahib L, Wehner MR, Matrisian LM, et al.

JAMA Netw Open 4: e214708, 2021

Key Points

Question: How will the landscape of cancer incidences and deaths change in the next 2 decades?

Findings: In this cross-sectional study, the results estimate that leading cancer incidences and deaths in the US will be notably different in the year 2040 vs. current rankings. Estimates included increases in melanoma incidence and deaths from pancreatic and liver cancer, and decreases in prostate cancer (PCa) incidence and breast cancer deaths.

Meaning: These estimates will be important to guide research, health care, and health policy efforts and emphasize the importance of cancer screening, early detection, and prevention.

Importance: Coping with the current and future burden of cancer requires an in-depth understanding of trends in cancer incidences and deaths. Projecting these trends will be important to guide future research funding allocations, health care planning, and health policy.

Objective: To estimate cancer incidences and deaths in the US to the year 2040.

Design and Setting: This cross-sectional study's estimated projection analysis used population growth projections and current population-based cancer incidence and death rates to calculate the changes in incidences and deaths to the year 2040. Cancer-specific incidences and deaths in the US were estimated for the most com-

mon cancer types. Demographic cancer-specific delay-adjusted incidence rates from the Surveillance, Epidemiology, and End Results Program were combined with US Census Bureau population growth projections (2016) and average annual percentage changes in incidence and death rates. Statistical analyses were performed from July 2020 to February 2021.

Main Outcomes and

Measures: Total cancer incidences and deaths to the year 2040.

Results: This study estimated that the most common cancers in 2040 will be breast (364,000 cases); second melanoma (219,000 cases); third lung (208,000 cases); fourth colorectal (147,000 cases);

PCa drops to the fourteenth most common cause of cancer (66,000 cases). Lung cancer (63,000 deaths) was estimated to continue as the leading cause of cancer-related death, with pancreatic cancer (46,000 deaths) and liver and intrahepatic bile duct cancer (41,000 deaths) surpassing colorectal cancer (34,000 deaths) to become the second and third most common causes of cancer-related death, respectively. Breast cancer (30,000 deaths) was estimated to decrease to the fifth most common cause of death.

Conclusions and Relevance:

Findings suggest that there will be marked changes in the landscape of cancer incidence and deaths by 2040.

Healthy Lifestyle May Offset Genetic Risk in Prostate Cancer *(Continued from page 1)*

sionals Follow-up Study. Men were divided into quartiles according to genetic risk.

The investigators also classified the men using a validated lifestyle score. For this score, one point was given for each of the following: not currently smoking or having quit 10 or more years ago, body mass index under 30 kg/m², high vigorous physical activity, high intake of tomatoes and fatty fish, and low intake of processed meat. Men with 1-2 points were considered the least healthy, those with 3 points were moderately healthy, and those with 4-6 points were considered the healthiest.

The outcomes assessed were overall PCa and lethal PC (i.e., metastatic disease or PCa-specific death).

At a median follow-up of 18 years, 2,111 cases of PCa cancer were observed. After

a median follow-up of 22 years, 238 lethal PCa events occurred.

Men in the highest genetic risk quartile were 5 times more likely to develop PCa (Hazard Ratio [HR], 5.39; 95% confidence interval [CI], 4.59-6.34) and 3 times more likely to develop lethal PCa (HR, 3.43; 95% CI, 2.29-5.14), vs. men in the lowest genetic risk quartile.

Adherence to a healthy lifestyle did not decrease the overall risk of PCa (HR, 1.01; 95% CI, 0.84-1.22), nor did it affect men in the lower genetic risk quartiles.

However, healthy lifestyle did appear to affect men in the highest genetic risk quartile. Men with the highest healthy lifestyle scores had roughly half the risk of lethal PCa when compared with the men with the lowest lifestyle scores (3% vs. 6%).

Plym observed that the rate of lethal disease in men with the best lifestyle scores matched the rate for the study population as a whole (3%), suggesting that healthy lifestyle may counterbalance high genetic risk.

She added that previous research has confirmed physical activity as a protective factor, but more study is needed to shed light on the relative benefit of the healthy lifestyle components. In addition, further research is needed to explain why the benefit was limited to lethal PCa risk in men with the highest genetic risk.

Plym speculated that genetic variants contributing to a high PRS may also be the variants that have the strongest interaction with lifestyle factors. "For men with a genetic predisposition to PCa," she added, "these

findings underscore the potential value of surveillance.

"Our findings add to current evidence suggesting that men with a high genetic risk may benefit from a targeted PCa screening program, aiming at detecting a potentially lethal PCa while it is still curable," she said.

Charles Swanton, MBPhD, of the Francis Crick Institute and UCL Cancer Institute in London, raised the possibility that competing risk issues could be at play.

"If a healthy lifestyle leads to longer life," he asked, "does that make it more likely that patients will live long enough to die from their PCa because they are not dying from cardiovascular disease, complications of diabetes, etc.? In that case, is the healthy lifestyle really affecting PCa at all?"

(Continued on page 8)

More Benefit with Taxane for Aggressive Metastatic Prostate Cancer *(Continued from page 1)*

survival (OS) of approximately 3 years,” the authors noted. However, a subset of men with adverse clinical features had worse outcomes. The adverse features included visceral metastases, rapid progression on androgen deprivation therapy (ADT), performance status, and elevated lactate dehydrogenase and alkaline phosphatase.

“Optimal first-line treatment for poor-prognosis mCRPC remains undetermined,” the authors continued. “Some evidence suggests that aggressive cancers might be less dependent on androgen receptor (AR) signaling. For example, somatic defects in RB1, TP53, and AR genes enrich for poor prognosis and poor outcomes with ARPI. However, this does not preclude response to taxane-based therapy.

“In general, ARPIs are the preferred first-line therapy for mCRPC because of proven survival benefits and tolerability,” they stated. Consensus guidelines for poor-prognosis mCRPC have suggested upfront chemotherapy, but the recommendation has limited clinical evidence support.

To investigate a potential preferred first-line treatment sequence, authors conducted a multicenter randomized trial limited to men with poor prognosis mCRPC and no prior exposure to an ARPI. Men received either cabazitaxel plus prednisone or investigator’s choice of abiraterone or enzalutamide plus prednisone. Granulocyte colony stimulating factor (GCSF) was allowed but not mandated.

Treatment continued until disease progression, unacceptable toxicity, or withdrawal of patient consent.

Progression was defined as a two-level or greater increase in performance status or change in cancer therapy for worsening cancer-related symptoms, PSA progression, or radiologic (X-ray) progression. Crossover to the alternate therapy was allowed at progression, provided that the patient continued to meet eligibility criteria.

The primary endpoint was composite investigator assessed CBR (PSA decline $\geq 50\%$, measurable X-ray response, or stable disease for ≥ 12 weeks in the absence of other indicators of disease progression. At investigator’s discretion, men with PSA progression only could continue treatment.

Data analysis comprised 95 randomized patients with a median follow-up of 21.9 months. The primary-endpoint analysis showed that men treated with caba-

zitaaxel had superior CBR ($P=0.039$, *a statistically significant difference*). Men randomized to cabazitaxel had a median OS of 37.0 vs. 15.5 months with an ARPI (a 42% reduction in the survival hazard for the cabazitaxel arm), but the difference did not achieve statistical significance ($P=0.073$). Median PFS with cabazitaxel vs. an ARPI was 5.3 vs. 2.8 months, respectively (Hazard Ratio [HR] 0.87, $P=0.52$).

First-line grade ≥ 3 treatment-related adverse events that occurred more often with cabazitaxel were neutropenia (32 vs. 0%), diarrhea (9 vs. 0%), and infection (9 vs. 0%). Biomarker analysis showed that a baseline ctDNA above the median and on-treatment ctDNA increase predicted a shorter time to disease progression (HR 2.38, $P<0.001$ and HR 4.03, $P<0.001$). Baseline ctDNA fraction $>30\%$

ctDNA was associated with markedly worse OS as compared with men who had undetectable baseline ctDNA (HR 38.22, $P<0.001$).

“The study provided evidence to support clinicians’ intuition favoring chemotherapy as initial treatment for men with aggressive mCRPC and no prior exposure to an ARPI,” said Moshe Ornstein, MD, of the Cleveland Clinic. “Many of us in the field intuitively think of using chemotherapy for patients who we consider as having more aggressive disease, but having randomized data to support it is important,” he stated. “Patients who might otherwise be given ARPI should at least be considered for a taxane-based chemotherapy, especially if they have a more aggressive phenotype... The initial clinical benefit is important for patients.”

MedPage Today
12 April 2021

Patient-Reported Health Status, Comorbidity Burden, and Prostate Cancer Treatment

McMahon S, Basak R, Zhou X, et al.

Urology 149: 103-109, 2021

Objective: To determine whether patient-reported health status, more so than comorbidity, influences treatment in men with localized prostate cancer (PCa).

Methods: Using Surveillance, Epidemiology, and End Results data linked with Medicare claims and CAHPS surveys, we identified men aged 65-84 diagnosed with localized PCa from 2004 to 2013 and ascertained their National Cancer Institute (NCI) comorbidity score and patient-reported health status. Adjusting for demographics and cancer risk, we examined the relationship between these measures and the treatments given to the overall cohort, low-risk men aged 65-74, intermediate/high-risk

men aged 65-74, and men aged 75-84.

Results: Among 2,724 men, 43.0% rated their overall health as Excellent/Very Good, while 62.7% had a comorbidity score of 0. Beyond age and cancer risk, patient-reported health status was significantly associated with treatment. Compared to men reporting Excellent/Very Good health, men in Poor/Fair health less often received treatment (odds ratio [OR] 0.71, 95% confidence interval [CI] 0.56-0.90). Younger men with intermediate/high-risk cancer in Good (OR 0.60, 95% CI 0.41-0.88) or Fair/Poor (OR 0.49, 95% CI 0.30-0.79) health less often underwent prostatectomy vs. radiation compared to men in Excellent/Very Good health. In contrast,

men with NCI comorbidity score of 1 more often received treatment (OR 1.37, 95% CI 1.11-1.70) compared to men with NCI comorbidity score of 0.

Conclusion: Patient-reported health status drives treatment for PCa in an appropriate direction, whereas comorbidity has an inconsistent relationship. Greater understanding of this interplay between subjective and empiric assessments may facilitate more shared decision-making in PCa care.

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Jump in Cancer Diagnoses at 65 Implies Patients Wait for Medicare, According to Study

A couple of years ago, Joseph Shrager, MD, professor of cardiothoracic surgery at Stanford School of Medicine, noticed a statistical anomaly in his practice. It seemed that patients were diagnosed with lung cancer at a surprisingly higher rate at 65 years old than, say, at 64 or 66.

He talked it over with his thoracic surgeon colleagues who said they were seeing something similar. They wondered if the jump in diagnoses might be due to patients delaying care until they became Medicare eligible at 65. "If this were true, and patients were delaying screenings or treatments for cancer, it could impact their survival," Shrager said. A quick exploratory analysis of their own practices showed a two-fold increase in lung cancer surgeries in 65-year-olds vs. 64-year-olds. "We decided to explore this, and its broader implications, in a larger population," Shrager said.

In the study published online March 29 in the journal *Cancer*, the researchers found a substantial rise nationwide in new diagnoses at 65 – not only for lung cancer but also for breast, colon, and prostate cancer (PCa) – the 4 most common in the U.S.

Researchers analyzed data from a national database of patients who were 61-69 years old and were diagnosed with lung, breast, colon, or PCa from 2004 to 2016. Patients included 134,991 with lung cancer, 175,558 with breast cancer, 62,721 with colon cancer and 238,823 with PCa.

There was a greater jump in cancer diagnoses at the transition from 64 to 65 than at all other age transitions, the research showed. Lung cancer rates consistently increased 3-4% each year for

people aged 61 to 64, then at 65 that percentage doubled. The increase was even more pronounced in people with colon cancer, which showed an annual growth rate of just 1-2% in the years leading up to Medicare eligibility, then jumped to nearly 15% at 65. In the years following age 65, diagnosis rates declined for all cancers, the study found.

The study showed that uninsured cancer patients (lung, breast, colon, prostate) older than 65 are more likely to undergo surgical intervention, and they had lower 5-year cancer-specific mortality rates than did their younger uninsured counterparts.

"Collectively, these results demonstrate that Medicare eligibility, an event coincident with becoming 65 years old, is associated with a rise in early-stage cancer diagnoses and a resulting survival benefit," authors concluded.

The researchers proposed that a number of factors cause 61- to 64-year-olds to wait for medical treatments and screenings until Medicare eligibility kicks in.

"These individuals often lack insurance as a result of early retirement, pre-existing conditions hindering renewal, the high cost of private insurance and other causes," the study said, noting that 13-

25% of this group of adults are uninsured or have a gap in medical coverage at some point preceding eligibility.

"Prior research shows that medical insurance is a strong predictor of receiving appropriate care, promoting earlier diagnosis and improved outcomes," the study noted.

"If you don't get the right screening or prompt diagnosis you are going to have lower cure rates," Shrager said. "This study underlines the important difference that some sort of Medicare expansion could make."

*Stanford University Medical Center
31 March 2021*

Inadequacies in Genetic Testing Referrals and Counseling in Prostate Cancer

Suri Y, Nandagopal L, Basu A

J Clin Oncol 38 (suppl 29): 43, 2020

Background: Recent studies recognize the high prevalence of germline mutations in genes affecting DNA repair in men with prostate cancer (PCa). In recognition of their growing clinical significance, the NCCN (National Comprehensive Cancer Network) guidelines recommend genetic counselling (GC) in PCa patients with certain risk factors. The application of these guidelines in clinical practice were evaluated.

Methods: All new clinic visits of PCa patients at UAB (University of Alabama at Birmingham) from January 2019 to June 2019 were identified and analyzed. We constructed a flow diagram of the UAB two-step referral model, performed a chart review, and analyzed the new clinic visits. We then sent a 10-item questionnaire to providers at UAB to collect information on germline genetic testing patterns, general approach to testing, and the barriers of GC, and actions to overcome barriers.

Results: From January to June 2019, 57 new PCa patients were seen, of which 23 had metastatic disease, 20 had high- or intermediate-risk localized disease, and the remaining had biochemical recurrence. In total, 38 men had an indication for GC. The most common indication was metastatic disease in 23 (40%) and localized high-risk in 15 (26%). Significantly, 33% of 24 patients with early onset PCa < 60 years did not meet NCCN defined criteria for testing. Only 39% of the 38 eligible men were referred, with testing completed in 11% of those with indications. The response rate to the survey was 91%; 30% of respondents reported that they would be comfortable completing GC themselves, and the most reported barrier to providing the testing themselves was time, and lack of expertise/experience. 70% of providers cited that lack of genetics workforce was a barrier to genetic testing, and 60% cited lack of

knowledge of genetic testing and genetics and the inadequate coordination of referrals were barriers.

Conclusions: While most PCa patients seen in the oncology clinic meet criteria for GC, referrals are inconsistent, and only a handful of eligible patients complete testing. From the survey results, the areas that need to be improved from the provider's side are education and comfort with genetic testing. From a systems perspective, the need for more genetics workforce, and better process workflows are required to improve the uptake of genetic testing referral and testing. The interventions of practice transformation and education need to be implemented and tested at UAB to improve adherence to the NCCN guidelines for genetic testing of PCa.

**Check Out the Us TOO
Advanced Prostate
Cancer Brochure at:**

www.us-too.org/AdvancedBrochure

Benefit, Harm, and Cost-Effectiveness Associated with Magnetic Resonance Imaging Before Biopsy in Age Based and Risk Stratified Screening for Prostate Cancer

Callender T, Emberton M, Morris S, Pharoah PDP, Pashayan N

JAMA Netw Open 4: e2037657, 2021

Importance: If magnetic resonance imaging (MRI) mitigates the overdiagnosis of prostate cancer (PCa) while improving the detection of clinically significant cases, including MRI in a screening program for PCa could be considered.

Objective: To evaluate benefit-harm profiles and cost-effectiveness associated with MRI before biopsy compared with biopsy-first screening for prostate cancer using age based and risk stratified screening strategies.

Design, Setting, and Participants: This decision analytical model used a life-table approach and was conducted between December 2019 and July 2020. A hypothetical cohort of 4.48 million men in England aged 55 to 69 years were analyzed and followed-up to 90 years of age.

Exposures: No screening, risk stratified screening, and age based screening in the hypothetical cohort. Age based screening consisted of PSA screening every 4 years in men between the ages of 55 and 69 years. Risk stratified screening used age and polygenic risk profiles.

Main Outcomes and Measures: The benefit-harm profile (deaths from PCa, quality-adjusted life-years [QALY], overdiagnosis, and biopsies) and cost-effectiveness (net monetary benefit, from a healthcare system perspective) were analyzed. Both age based and risk stratified screening were evaluated using a biopsy-first and an MRI-first diagnostic pathway. Results were derived from probabilistic analyses and were discounted at 3.5% per annum.

Results: The hypothetical cohort included 4.48 million UK men, ranging in age from 55 to 69 years (median, 62 years). Compared with biopsy-first, age based screening, MRI-first age based screening was associated with 0.9% (1,368; 95% uncertainty interval [UI], 1,370-1,409) fewer deaths from PCa, 14.9% (12,370; 95% UI, 11,100-13,670) fewer overdiagnoses, and 33.8% (650,500; 95% UI, 463,200-907,000) fewer biopsies. At 10-year absolute risk thresholds of 2% and 10%, MRI-first risk stratified screening was associated with between 10.4% (7,335; 95% UI, 6,630-8,098) and 72.6% (51,250; 95% UI, 46,070-56,890) fewer overdiagnosed cancers, respectively, and between 21.7% fewer MRIs (412,100; 95% UI, 411,400-412,900) and

53.5% fewer biopsies (1,016,000; 95% UI, 1,010,000-1,022,000), respectively, vs. MRI-first age-based screening. The most cost-effective strategies at willingness-to-pay thresholds of US \$26,000 and \$39,000 per QALY gained were MRI-first risk-stratified screening at 10-year absolute risk thresholds of 8.5 and 7.5%, respectively.

Conclusions and Relevance: In this decision analytical model of a hypothetical cohort, an MRI-first diagnostic pathway was associated with an improved benefit-harm profile and cost-effectiveness of PCa screening vs. biopsy-first screening. Improvement was greater when using risk stratified screening based on age and polygenic risk profile and may warrant evaluation in prospective studies.

Research Uncovers Additional Treatment Option in Prostate Cancer

The standard treatment for advanced metastatic prostate cancer (PCa) is androgen deprivation therapy (ADT). However, 1/3 of men will become resistant and develop castration-resistant PCa cancer (CRPC). A new study, by Karolinska Institutet and others, shows that estrogen receptor beta (β ; ER β) agonists together with ADT could be a useful treatment. ADT is based on the use of hormones to cause chemical castration and is the usual treatment of metastatic PCa. And even if this is an efficient way to treat PCa in the short term, some will build up a resistance to ADT and develop fatal CRPC. For this reason, there is a clear need for alternative treatments. ER β is a tumor suppressor

and its role in PCa treatments and prevention has been investigated for more than 20 years. ER β expression is lost as PCa progresses. But a new study published in the *Proceedings of the National Academy of Sciences* (PNAS), by Karolinska Institutet, University of Houston, University of Texas MD Anderson Cancer Center and Barmherzige Schwestern Hospital shows that the nuclear transport of epidermal growth factor receptor (EGFR) could be a target of ER β agonist treatment.

Immunochemical staining of sequential sections in tissue arrays indicated that ER β was expressed in both luminal and basal prostate epithelial cells. But the androgen receptor (AR) was only expressed in luminal cells and

not in basal cells. This is the reason why ADT can prevent the spread of AR-positive cancer cells but has no effect on basal cells.

Increased EGFR nuclear translocation seen with finasteride is markedly reduced by adding ER β agonist, isoflavone, suggesting it may prevent onset of tyrosine kinase driven cancers.

"This study provides further evidence that ER β agonists may be a good medicine vs. certain forms of PCa," says Professor Jan-Åke Gustafsson at the Department of Biosciences and Nutrition, KI. "This is a line of research that we intend to continue working with."

Karolinska Institutet
29 March 2021

Join a Virtual Prostate Cancer Support Group

While we all must remain safe and socially distant due to COVID-19 restrictions, it is important for everyone to continue to monitor and address their health concerns, and stay connected to others. Us TOO has virtual prostate cancer support groups that continue to meet regularly and host guest speakers. These meetings can be accessed by phone or by internet, and can be attended from any location. For a list of groups, please visit:

www.ustoo.org/virtual-ustoo-support-groups

Magnetic Resonance Imaging-Targeted and Systematic Biopsy for Detection of Grade Progression in Patients on Active Surveillance for Prostate Cancer

Yerram NK, Long L, O'Connor LP, Wang AZ, Ahdoor M, et al.

J Urol 205: 1352-1360, 2021

Purpose: Active surveillance (AS) for patients with low- and intermediate-risk prostate cancers (PCa) is becoming a more utilized option in recent years. However, the use of magnetic resonance imaging (MRI) and imaging-targeted biopsy for monitoring grade progression has been poorly studied in this population. We aim to define the utility of MRI-targeted biopsy and systematic biopsy in an AS population.

Materials and Methods: Between July 2007 and January 2020, patients diagnosed with PCa who elected AS were monitored with prostate MRI, imaging-targeted biopsy and standard systematic biopsy. Patients were eligible for surveillance if diagnosed with any volume Gleason grade 1 disease and select Gleason grade 2 disease. Grade progression

(Gleason grade 1 to ≥2 disease and Gleason grade 2 to ≥3 disease) for each biopsy modality was measured at 2 years, 4 years, and 6+ years.

Results: In total, 369 patients had both MRI-targeted and systematic biopsy and were surveilled for at least 1 year. At 2 years, systematic biopsy, MRI-targeted biopsy and combined biopsy (systematic + imaging-targeted) detected grade progression in 44 patients (15.9%), 73 patients (26.4%) and 90 patients (32.5%), respectively. MRI-targeted biopsy detected more cancer grade progression compared to systematic biopsy in both the low- and intermediate-risk populations (p <0.001). Of all 90 grade progressions at the 2-year time point, 46 (51.1%) were found by MRI-targeted biopsy alone and missed by systematic biopsy.

Conclusions: MRI-targeted biopsy detected significantly more grade progressions in our AS cohort compared to systematic biopsy at 2 years. Our results provide compelling evidence that prostate MRI and imaging-targeted biopsy should be included in contemporary active surveillance protocols.

Genetic Risk of PCa

(Continued from page 4)

Plym responded that, among those in the highest genetic risk group with an unhealthy lifestyle, the increased risk for prostate cancer exceeded the risk for other illnesses.

Presented at the 2021 AACR Annual meeting, abstract 822
Medscape Medical News
15 April 2021

Prostate RT

(Continued from page 1)

prostate RT in this cohort was associated with a clinically significant OS improvement."

The authors noted that their cohort predated the debut of docetaxel and potent androgen receptor pathway inhibitors for use in mHSPC.

"Whether the benefit of prostate RT in mHSPC will persist when used in addition to these therapies – or indeed, be enhanced by co-administration with these therapies – awaits the results of trials in progress."

Renal & Urology News
19 April 2021

Video is now available of our March 25th webinar on **Diet-Related Health Disparities Within the Black Community**

View the video at:
www.ustoo.org/ustoo-video

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Between the Sheets...

May 2021

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. Jeffrey Albaugh, PhD, APRN, CUCNS, Director of Sexual Health at NorthShore University HealthSystem and at Jesse Brown VA Medical Center in Chicago, IL. Dr. Albaugh is a board-certified advanced practice urology clinical nurse specialist, certified sexuality counselor and trained relationship counselor. He has completed Level 1 and 2 training from the Gottman Institute and has also trained with Andrew Christensen, PhD in Integrative Behavioral Couples Therapy. In addition to his many publications in peer reviewed journals and chapters in books on sexual dysfunction, Dr. Albaugh published *Reclaiming Sex and Intimacy After Prostate Cancer Treatment*. He has been quoted in media and publications as an expert in the treatment of sexual dysfunction.

QUESTION FROM PROSTATE CANCER SURVIVOR:

I don't notice much difference between generic sildenafil and Viagra. Is there a difference? Why can't I take more than 100mg?

RESPONSE FROM DR. JEFFREY ALBAUGH:

Thank you for your questions. Both generic sildenafil and Viagra contain the same chemical: sildenafil. They are the same chemical and should work equally in most men. I have worked with many men who have alternated between branded and generic sildenafil. Some of these men were taking both because insurance allows them a few a month and they use generics the rest of the time (due to the drastic cost difference). Men tell me all the time that they find no difference in the generic versus the branded version of sildenafil. Once in a while, a patient may complain about a particular side effect with one over the other and this is likely due to the other components of the pill (not the chemical of sildenafil, but the other substances in that particular pill). You should expect to get the same results with the generic versus the branded version of sildenafil. If you haven't used a discount coupon program like www.goodrx.com, it can be helpful in finding the lowest price at the pharmacies in your particular area. Sildenafil can cost as little as 30-50 cents a pill through those programs (versus up to about \$75 a pill in the past for branded pills). The same discount type programs can be used for other generic phosphodiesterase type 5 inhibitors (PDE-5i) with just as good of savings on generic tadalafil (the chemical of Cialis) and men find that generic tadalafil works as well as the branded medication.

It is not recommended that you take more than the highest FDA approved dose of sildenafil, which is 100mg. The studies done with sildenafil show the benefits most outweigh the risks if you stay within that maximum dose. Higher doses could lead to more side effects. The most concerning side effects are lowering of the blood pressure and, thereby, possibly raising the heart rate. Remember these PDE-5is were designed to lower the blood pressure, initially, and then were discovered to help with erections. They do slightly lower the blood pressure at the FDA approved doses, but may lower the blood pressure more substantially at higher doses. As the blood pressure is lowered, the heart rate may increase, which is again of concern. The same concerns would hold true for any of the other PDE-5is (tadalafil, vardenafil and avanafil). Remember dosing is different for these other medications. For example, tadalafil is dosed at 5-20mg, so the highest FDA approved dose of tadalafil is 20mg, and that would be equivalent to sildenafil 100mgs. In general, you should be careful not to drink 3 or more equivalent units of alcohol with PDE-5is as that may lower your blood pressure, and also will not help your erectile function. It is important to work carefully with your prescriber to make sure you safely use each of these medications, especially in regard to other medications you may take that may interact with these medications.

You can access the new edition of my book at www.drjeffalbaugh.com.

Watch Dr. Albaugh's presentation on sexual health and intimacy from the *Prostate Cancer Pathways for Patients and Caregivers* event recorded at NorthShore University HealthSystem in Skokie, IL on November 3, 2018 at <https://www.youtube.com/watch?v=Hiq0dDEb1I0&t=4483s>.

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

Pssst!
Check out our
feature on sex and intimacy,
Between the Sheets...

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).

Benefits of a Healthy Lifestyle in Men at High Risk of Prostate Cancer

Can a healthy lifestyle compensate for genetic risk of prostate cancer? A new study shows promise.

As the saying goes about cancer and other diseases, "Genetics loads the gun, and environment pulls the trigger." Some men are at higher risk of prostate cancer because of the genes inherited from their parents. That can't be changed. For prostate cancer, "environment" can include lifestyle factors like smoking, not exercising, and an unhealthy diet.

The good news is, men may be able to offset their genetic risk for prostate cancer with a healthy lifestyle. This was shown in a new PCF-funded study (<https://www.abstractsonline.com/pp8/#!/9325/presentation/1890>) by Lorelei Mucci, ScD, MPH, of the Harvard T. H. Chan School of Public Health, and team, presented in April at the American Association for Cancer Research 2021 Annual Meeting.

First, the research team applied a "polygenic risk score" (<https://www.pcf.org/c/new-genetic-test-could-be-the-ultimate-in-early-detection>) — a score previously developed by PCF-funded team led by Christopher Haiman, to calculate a person's prostate cancer lifetime risk based on their genetics. This score was applied to more than 10,000 men who had been followed for 20 years. The researchers found that men with the highest polygenic risk score were more than 5 times as likely to be diagnosed with prostate cancer, and more than 3 times more likely to die from prostate cancer, than men with the lowest polygenic risk score.

The team also had information about lifestyle, and calculated a "lifestyle score" (<https://pubmed.ncbi.nlm.nih.gov/26577654>) based on 6 factors: not smoking, BMI < 30, exercising, high intake of tomatoes and fatty fish, and low intake of processed meat. More points is better, so 4-6 points was defined as a "healthy lifestyle."

Then, researchers looked at the relationship between prostate cancer genetic risk score and lifestyle score. Among men with the greatest potential (based on genetics) to develop lethal prostate cancer, a "healthy lifestyle" was protective—those with a healthy lifestyle lowered their actual risk of lethal prostate cancer by 46%, compared to men with the least healthy lifestyle. Even a "moderately healthy" lifestyle helped, lowering risk of lethal prostate cancer by 41%.

What can men take away from this? You can't change your genes, but you can change what you eat and how much you exercise. While more research is needed, this study suggests that in men at high genetic risk for lethal prostate cancer, a healthy lifestyle may lower that risk. Even if you don't know your prostate cancer genetic risk—certainly, most men do not!—there's plenty of evidence (<https://www.pcf.org/c/the-best-of-the-best-food-science-and-prostate-cancer>) that quitting smoking, increasing exercise, and eating more brightly-colored vegetables improves your heart health and reduces your risk of cancer and other chronic diseases.

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