Chemoprevention of Prostate Cancer

"A Conversation with Paul Sieber, M.D."

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INTRODUCTION

We've all been taught that screening leads to early detection, which leads to early treatment, which, in a perfect world, leads to a good chance for a cure; right?

Not always.

Take prostate cancer, for example. The more we screen, the more positive reports we get, which may lead to unnecessary treatments, which leads to a good chance of creating some *extremely* undesirable side effects in otherwise healthy men. And as for a cure — once tumors start growing in the prostate, we can't seem to stop most of them from spreading.[1]

Despite such dire predictions, the effects of screening haven't been entirely devastating. For example, the number of men dying from this disease is actually starting to decline, and prostate cancer has fallen from the second leading cause of cancer-related death in men[2] to the third. Unfortunately, the number of men developing the disease for the first time remains high, with well over 200,000 new diagnoses each year and a prediction that this number will continue to rise.[3,4] Additionally, the burden of this disease remains, as always, primarily on older men and African-American men.[3]

How can we catch these tumors earlier and stop their growth? Obviously we can't do anything about age or genetics. And as for more screening — at best, that's "controversial." It looks like our best bet is to find out what triggers tumor formation in the prostate and find a drug that will put it out of action early.

THE SEARCH FOR BIOMOLECULAR TRIGGERS

Several potential markers for prostate cancer have already been identified and are the basis for several ongoing clinical trials. They're quite diverse — increased androgen activity, decreased estrogen activity, an inadequate diet, chromosomal changes in premalignant lesions. But they seem to share two mechanisms of action: oxidative stress and abnormal genetic translation.

PROSTATE ENEMY #1: OXIDATIVE STRESS

Clues to the role of oxidative stress in prostate cancer were found in a couple of nutrition studies: the ATBC (α-Tocopherol and β-Carotene) study, which studied whether vitamins E and A can reduce the risk for lung cancer, and the Nutritional Prevention of Cancer Study, which studied whether selenium reduces the risk for skin cancer.[5,6] They didn't find what they were looking for, but they did find that *all 3 nutrients reduce the incidence of prostate cancer.*[2]

These nutrients share a common mechanism of action: *antioxidant activity.* A shortage of antioxidants (i.e., oxidative stress) leaves free radicals "free" to interact with DNA and promote carcinogenesis. Androgens might contribute to this problem; they've been observed triggering the release of free radicals in human prostate cancer cell lines.[2] This problem could be solved by blocking androgen activity — which means blocking 5-α reductase activity to prevent the conversion of testosterone into dihydrotestosterone, which actually carries out androgen activities.[7] If we can do that effectively, we might just find ourselves on the road to a cure.

PROSTATE ENEMY #2: A BAD TRANSLATION

Changes in gene expression (e.g., to reduce apoptosis) and structure (e.g., increased methylation) may allow normal epithelial prostate tissue to progress to premalignant tissue, then to local adenocarcinoma, and finally to metastatic disease.[2] If we could identify the specific genes or gene products that are affected, perhaps we could use them as markers to stage prostate cancer more accurately.

THE SEARCH FOR TRIGGER BLOCKERS

Four key clinical trials have been designed to evaluate several methods of blocking cancer triggers in the prostate: PCPT (Prostate Cancer Prevention Trial), the REDUCE (Reduction by Dutasteride of Prostate Cancer Events) Study, SELECT (Selenium and Vitamin E Cancer Prevention Trial), and PIN (Prostate Cancer Prevent Study for Men With High-grade Prostatic Intraepithelial Neoplasia [PIN]).

One of Lancaster General's own, Dr. Paul Sieber, has participated in all four studies.

PCPT

PCPT was a 7-year, phase 3, randomized, double-blind, placebo-controlled trial of finasteride (Proscar) — which inhibits type 2 5α-reductase — in 18,882 healthy men aged 55 years and older.[4] This study was terminated 2 years early, when the investigators found that the incidence of prostate cancer had dropped by close to 25% in men taking finasteride.[8] That would mean that 316,760 person-years could be saved with this drug. But don't be too impressed: The finasteride group also had very aggressive tumors (Gleason scores: 7-10), enough to reduce the number of person-years saved by close to 40,000.[9]

Dr. Sieber was not impressed at all by PCPT. Currently chief of the Division of Urology at Lancaster General, Sieber was a "young" doctor when the PCPT team started enrolling men in 1993.[4] But even now, with 85 clinical trials under his belt, he's bothered by the trial's study design. The first problem: the enrollment criteria. Every man had to have a PSA of 3 ng/mL to be enrolled, but digital rectal exams (DREs) and biopsies were not required.[8] Failure to use the DRE is a major concern, because "the physical exam has always been notorious for either underestimating or overestimating prostate cancer," he explained. "What bothered me the most about the study design was that they didn't biopsy everybody when they started." The PCPT team may have assumed that a normal PSA and a normal DRE meant a normal exam. But Dr. Sieber points out that " 'Normal' at that time is now viewed with some skepticism." For example, a PSA reading of 4 to 10 ng/mL was considered a diagnostic "grey zone" in the early 1990s. The current cutoff is 3 ng/mL for everyone preferably tailored to the age of the man.[3] And consider the changes in biopsy technique. "We used to take 6 cores for a biopsy," he explained, "and now we take 12 cores." As a result, the diagnostic rate has increased dramatically. Thus, while using what were state-of-the-art techniques in their time, the PCPT team may have missed a lot of cancer over the years.

This is a drawback for most long-term studies. Techniques can become outmoded before the study ends, making its findings less useful. That's why the REDUCE study was developed—to "correct" some of the shortcomings of PCPT.

REDUCE

The REDUCE study is a 4-year, international, double-blind, placebo-controlled trial of dutasteride (Avodart) 0.5 mg daily in men aged 50 to 75 years.[10] The most obvious improvement in this trial over PCPT is that a biopsy is scheduled every 2 years, in addition to the one required before enrollment. Another important improvement is the "staging" of PSA cutoffs by age: 2.5 to 10 ng/mL for men aged 50 to 60 years and 3.0 to 10 ng/mL for those older than 60.[9]

Yet another improvement is the choice of drug. Dr. Sieber (who is on the advisory board for this study) admits to questioning the advisability of studying a 5-α reductase in PCPT, because at that time this enzyme was thought to be present in the stroma of the prostate and not in glandular tissue, where prostate cancer originates. Given the knowledge base at that time, the idea of studying a 5-α reductase inhibitor seemed like "a joke."

No one's laughing now.

It turns out that 5-α reductase really is found in the glandular tissue, as it's upregulated in prostate cancer. It also turns out there are 2 of them — types 1 and 2.[10] That's why the REDUCE team decided to study dutasteride, which, like finasteride, is a 5-α reductase inhibitor, but unlike finasteride — which targets the only 5-α reductase known at that time (type 2) — dutasteride targets both and, consequently, causes DHT levels to fall must lower than finasteride (90% vs 70%). A good move — since there might be more type 1 5-α reductase in malignant tissue than in benign tissue.[9]

SELECT

SELECT is based on the findings of the 2 failed nutrition studies mentioned previously — ATBC and the Nutritional Prevention of Cancer Study — which revealed that α-tocopherol (vitamin E), β-carotene (vitamin A), and selenium reduce the risk for prostate cancer.[5,6]

SELECT is a 7- to 12-year, multinational, phase 3, randomized, placebo-controlled trial of selenium 200 µg daily, vitamin E 400 IU daily, or combination therapy to see if these supplements can reduce the incidence of prostate cancer.[4] In 2001, this trial started recruiting men aged at least 50 years (African Americans) or 55 years (non-African Americans) (goal: N = 32,400).[4]

Such a straightforward study — what could possibly be wrong with it?

Well, for one thing, PSAs and DREs are not required, except to enter the study. Neither are biopsies. "I'm the urologist of record for our SELECT trial," says Sieber. "I haven't seen a single patient… for a biopsy."

For another thing, SELECT doesn't take baseline selenium readings. Those are difficult to get, anyway, especially for a nutrient like selenium whose levels in soil vary geographically.[6] Second, selenium has a nonlinear relationship with its antioxidative effects[11] — so more is not necessarily better, it might be downright toxic. Third, nutrition studies tend to have the best results in patients who are already malnourished. In fact, the initial "hint" at selenium's cancer-fighting qualities was seen in a study conducted in a part of the world were the availability of fresh fruits and vegetables has historically been low.[4,6] Fourth, it's hard to know how much of a nutrient is already in the diet, unless "you have people living in a lab like a rat and feed them the same meal," quips Sieber.

On the other hand, SELECT has the highest participation of African Americans of any prostate cancer study — 15% compared with the single-digit percentages for total minority enrollment in similar studies.[4] Given that African-American men tend to have the most severe cases of prostate cancer,[3] Sieber applauds their minority recruitment efforts. African-American enrollment is crucial for prostate cancer research. "When you look at blacks and Asians and whites [in terms of] their genetic diversity, whites are among the most monotonous by a long shot, and blacks are the most diverse," he explains. With low minority enrollments, drugs have been designed based on data gathered primarily in whites. Given the genetic diversity of African Americans, Sieber points out that "if you design a drug that seems to work great for whites, it may (only) work for a fraction of black patients."

PIN

The PIN team started recruiting men aged 30 years and older (goal: N = 1260) in 2005 for this 18-month trial of toremifene citrate (Fareston) 20 mg daily versus placebo to evaluate its effectiveness in preventing the progression of PIN to prostate cancer.[12] This drug is currently indicated for postmenopausal women with metastatic breast cancer.[13] In breast tissue, it seems to block estrogen activity — possibly by blocking one of two known estrogen receptors (ERs), specifically ER-alpha.[13] But there's a second ER (ER-beta), which seems to be dominant in the prostate and decreases in concentration during prostate cancer.[14] If this study works, it might be a result of toremifene serving as an agonist at ER-beta, more so than by serving as an antagonist at ER-alpha.

Sieber suggests that the premalignant status of PIN is controversial in the academic world, but in clinical practice, "there's no question that PIN and prostate cancer are associated [with each other]," adding that when he sees cancer on one side of the prostate and PIN on the other, cancer is almost always lurking on the second side.

WHAT'S NEXT?

Dr. Sieber mentioned a few things in passing that might very well become the foci of future studies:

Finding a role for inflammation. Chronic inflammation leads to oxidative stress, chronic inflammation is common in prostate biopsy specimens,[2] and, according to Sieber, "People who are regularly using antiinflammatories have less prostate cancer."

Finding a chemopreventive role for statins. "There's still [some] pretty hot [talk suggesting] that the prostate cancer risk goes down in people who take statins," he claims.

Finding a predictive biomarker. Dr. Sieber mentioned that prostate cancer doesn't have many biomarkers compared, say, to breast cancer. With men living longer, that means a slow-growing prostate tumor can reach a dangerous stage before it is detected. Sieber hopes to see biomarkers that can be used to predict cancer progression in specific patients over specific periods of time. With continued advances in molecular cytogenetic techniques, his wish may soon become reality.

Finding predictive histopathological tests. Finding a biomarker without having a useful way of monitoring seems like a waste of time. Fortunately, several immunohistochemical stains are already available that allow us to do just that. We already know they can be used to trace the loss of proteins that control the cell cycle, such as p27, and obtain prognostic information about cancer. Maybe someday such information can be coordinated with changes in tumor scores and other data to let us predict disease progression over time.

By satisfying this "wish list" and finding positive outcomes from the 4 trials described above, we may finally be able to offer vulnerable patients effective chemoprotection against prostate cancer. Will this happen in your lifetime? To quote Dr. Sieber: "We'll see."

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