

Is There a Future for Chemoprevention of Prostate Cancer?

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Abstract

The outcome of the Selenium and Vitamin E Cancer Prevention Trial, demonstrating harm and no preventive activity of selenomethionine and α -tocopherol for prostate cancer, and the lack of approval by the FDA for the use of 5 α -reductase inhibitors to prevent prostate cancer have cast doubt about the future of chemoprevention of prostate cancer. This article attempts to critically assess whether the notion that chemoprevention of prostate cancer has no future is warranted. Risk of prostate cancer is modifiable and chemoprevention of prostate cancer, particularly fatal/lethal cancer, is both needed and possible. However, the approach to prostate cancer-chemopreventive agent development has not

followed a rational and systematic process. To make progress, the following steps are necessary: (i) identification of intermediate biomarkers predictive of fatal/lethal disease; (ii) development of a rational approach to identification of candidate agents, including high-throughput screening and generation of information on mechanism and biology of candidate agents and potential molecular targets; and (iii) systematic evaluation of the predictive value of preclinical models, phase II trials, and intermediate biomarkers for the outcome of phase III trials. New phase III trials should be based on adequate preclinical and phase II studies. *Cancer Prev Res*; 9(8); 642-7. ©2016 AACR.

The Selenium and Vitamin E Cancer Prevention Trial (SELECT) was scientifically sound but conclusively demonstrated lack of preventive benefit of vitamin E and selenium on prostate cancer (1) and indicated possible harm of both α -tocopherol and selenomethionine (2, 3). Selenized yeast did not reduce prostate cancer risk in another randomized clinical trial (RCT; ref. 4), failing to reproduce the findings of the NPCT study (5). These outcomes have drawn a wide range of reactions, including negative ones; some have even declared chemoprevention of prostate cancer dead. For example, M.B. Garnick (Harvard Medical School; Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA) stated in an interview in Medscape Oncology "Chemoprevention of prostate cancer: Case closed" (6). The outcome of SELECT has even negatively impacted views on cancer chemoprevention in general (7). Although intervention with the 5 α -reductase inhibitors finasteride and dutasteride in the PCPT and REDUCE trials resulted in a 23% to 25% reduction in relative risk (8, 9), the FDA did not approve 5 α -reductase inhibitors for prevention of prostate cancer, and these agents are not clinically used to any significant extent as preventive agents (10).

Although a positive vision is typically portrayed in lessons learned from these clinical trials (11), it is important to critically assess whether statements and views that chemoprevention of prostate cancer has no future are warranted. In this commentary, I attempt to do so by answering several pertinent questions, rather than providing a review or proposing new preclinical or clinical research designs for prostate cancer chemoprevention.

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Is Prevention of Prostate Cancer at All Possible?

It appears reasonable to ask whether prevention of prostate cancer and death from this malignancy is at all possible. Although the answer is uncertain, there is evidence that strongly suggests that risk of prostate cancer is modifiable. Landmark migrant studies of men who moved from countries with a low risk of prostate cancer to the United States demonstrated that these men acquired the much higher U.S. risk, indicating that risk of prostate cancer is modifiable to a considerable extent, probably due to lifestyle changes (12-15). Although there are no studies of men who moved from high risk to low risk areas to demonstrate that reduction of risk by environmental factors is possible, these migrant studies support the idea that prostate cancer is preventable (12, 15). The outcomes of the PCPT and REDUCE trials provide further support for this notion.

What Needs to Be Prevented?

There is no consensus about what kind of prostate lesions need to be prevented, high-grade prostatic intraepithelial neoplasia (PIN), all invasive cancers, or only aggressive, potentially lethal cancers. Many biopsy-detected prostate cancers remain indolent and will never progress to clinically troublesome malignancies, whereas other cancers are aggressively growing and progressing at a rapid speed (16). The latter cancers are clearly clinically significant and should surely be prevented. However, prevention of clinically insignificant tumors may also be desirable because their detection often leads to morbidity-associated interventions. There is also no consensus about how to distinguish insignificant and significant prostate cancer and what the threshold between the two is. Furthermore, clinical practice, both for screening and early detection and for decisions about treatment versus watchful waiting, is constantly shifting, impacting outcomes of any RCT of prostate cancer chemoprevention.

Van der Kwast and Roobol (16) proposed an approach to defining the threshold for significant versus insignificant prostate cancer. They argued that age of onset, tumor aggressiveness, and age at death from other causes are the major factors that need to be taken into account when considering chemoprevention. Some cancers grow so fast that they cannot be prevented, regardless of the age of onset, whereas other tumors grow slower and will never become a clinical problem if they develop later in life; and many cancers will remain indolent and insignificant even if they are detectable as early as 30 to 40 years of age. It is reasonable to assume that there are not separate classes of prostate cancer, but that there rather is a continuum ranging from early- to late-onset tumors and from tumors that remain indolent to fast growing and progressing cancers. These considerations imply that chemoprevention should be aimed at preventing those cancers that develop early and have time to progress and particularly those cancer that are aggressive because they cause mortality. However, this idea is limited by (i) the age window in which chemoprevention can receive traction among men at risk, say from the age of 50, and can be effective, say until the age of 75, (ii) the growth rate of fast growing tumors, and (iii) the lack of consensus or insight regarding which tumors are significant and which are not, as indicated above. On the positive side, new prognostic molecular tools are probably going to help resolve some or many of these issues (17–20).

Why Have We Not Made Progress in Chemo- or Dietary Prevention of Prostate Cancer?

Chemoprevention of prostate cancer may indeed be dead and buried in the absence of a success story of an agent that truly does prevent prostate tumors that are potentially fatal. So, why have we not made progress toward such a success story? I would argue that this is, in large part, due to the fact that indirect evidence from epidemiology and from RCTs with prostate cancer as a secondary endpoint has been used to select candidate agents for large phase III trials in the absence of adequate preclinical data and phase II clinical studies. This was certainly the case for the phase III RCTs with selenium and vitamin E; there were no adequate phase II data and existing preclinical data suggested lack of efficacy and even risk of hazard for α -tocopherol (21, 22). Of note, for the RCTs with 5 α -reductase inhibitors, which did reduce risk but only of lower grade prostate cancers, there were a limited number of preclinical chemoprevention studies and adequate data on their biologic effects and their safety, although not all were published before the start of the phase III RCTs (23–28).

I want to argue that a traditional approach of drug development will serve us much better than relying on results of epidemiologic studies and of secondary analyses of RCTs for the selection of promising chemopreventive agents. Information about the biologic activities of candidate agents, identified from indirect epidemiologic and RCT evidence or on the basis of mechanistic data, can be used to move forward to relevant preclinical toxicity and chemoprevention efficacy studies, resulting in selection of promising agents for phase I and phase II studies. Only if those studies all point to low toxicity and considerable efficacy, one should move forward to phase III RCTs.

As I have recently pointed out (29), this approach to rational chemopreventive drug development can be successful, as was

shown for the prevention of colon cancer by a combination of the NSAID sulindac and the ornithine decarboxylase inhibitor difluoromethylornithine, first in experiments with a rat model (30, 31) and subsequently in a RCT (32), whose findings are further examined in two ongoing phase III trials. This approach was also successfully taken with 5 α -reductase inhibitors, although these disappointingly did not reduce risk of high-grade, aggressive cancers.

How to Identify Promising Candidate Chemoprevention Agents?

It is essential to first define prostate cancer features that are important in considering the overall approach to agent selection and efficacy testing. There is considerable evidence that there are multiple pathways of prostate carcinogenesis and a multitude of underlying carcinogenic mechanisms (33). Furthermore, prostate cancer is notorious for considerable biologic, clinical, and pathologic heterogeneity (34). The focus should be on prevention of aggressive lethal cancers and early-onset cancers, but these cannot be easily identified. These considerations point to the need for broad-spectrum chemopreventive agents or combinations of agents that target these various pathways, mechanisms, and variants of prostate cancer. Potter (7) also recently pointed to the need for such broad-spectrum agents.

Furthermore, multiple preclinical models should be used that represent different pathways and types of cancer and progression to lethality. Similarly, multiple designs and endpoints of phase II clinical trials focusing on different aspects of prostate cancer need to be developed and applied in parallel to identify agents that have considerable promise to have efficacy in humans, particularly to prevent fatal or aggressive prostate cancer. These issues are further discussed in the next two sections.

What Are the Best Preclinical Models?

There are no well-defined and validated high-throughput *in vitro* systems that could help identify promising agents, and there is also no information about which *in vitro* preclinical systems are most predictive of *in vivo* outcomes. Several preclinical prostate cancer models have been used for chemoprevention studies, but it is not clear which are most predictive of RCT outcomes, and there have hardly been any systemic attempts to validate these preclinical models. Prostate cancer cell lines have often been used in xenograft experiments to identify promising candidate agents. However, most of these cell lines were derived from advanced cancers and are thus not representative of earlier stages of prostate cancer development and may not be sensitive to agents that interfere with these stages.

Animal models are of course limited in their ability to represent human prostate cancer, but that does not negate their potential usefulness in identifying promising candidate chemoprevention agents that are of low toxicity. However, it is not clear which *in vivo* models are most predictive of phase II and III trial outcomes and which are most reflective of clinically significant prostate cancer in men. Genetically modified mouse models and prostate cancer induction models in rats have been employed. Because mouse models have not been used as widely and methodically as rat models, there is less information about the predictive value of mouse models. Some of the problems that have impeded use of mouse models include (i) difficulties in breeding sufficient

numbers of animals with correct genotype to allow adequate chemoprevention experiments, (ii) genetic alterations in these models that are often associated with later, not early stages of prostate cancer development (e.g., SV40 T-antigen) and often represent only one pathway, (iii) endpoints that are not always sufficiently well established (cancer, mPIN, metastases), and (iv) cancer incidence that can be overwhelmingly high (100%) or too low (35).

The methylnitrosourea (MNU) plus testosterone rat model (22, 36) has been used to systematically screen more than 20 candidate agents for efficacy using a standardized experimental protocol (21, 37–48). In this model, chemopreventive candidate agents are fed to rats, starting when chronic low-dose testosterone treatment is applied after MNU injection. Eight agents were efficacious in this model; 9-*cis*-retinoic acid and flutamide were most active, whereas dehydroepiandrosterone (DHEA), 16 α -fluoro-5-androsten-17-one (fluasterone), Bowman–Birk inhibitor, a soy isoflavone extract, celecoxib, and 13-*cis*-retinoic acid were less active. Importantly, two efficacious agents (9-*cis*-retinoic acid and DHEA) retained their activity when the start of the treatment was delayed as much as 20 to 40 weeks into the experiment (39, 43); other agents have not been tested in this delayed treatment protocol. None of these eight agents have been tested in RCTs and probably will not be tested ever because of safety concerns. This rat model was entirely predictive of the negative outcomes of the RCTs with selenium and vitamin E, including the increased risk of prostate cancer with the latter agent (21). Other agents tested in this model have not been studied in RCTs (49), but finasteride, which was active in the PCPT study, was also modestly preventive in a similar rat model (50). Selenium and vitamin E were also negative in some mouse models (51, 52).

What Are the Best Designs of Phase II Clinical Trials?

The short answer is, again, we do not know. A major problem is uncertainty about which phase II trial designs are most appropriate for predicting efficacy in phase III RCTs. Furthermore, accrual into phase II trials is often problematic. There is also uncertainty about which intermediate biomarkers are reliable indicators of chemopreventive efficacy and how to validate them. These factors have caused a bottleneck in conducting phase II RCTs.

There are no RCT designs that specifically predict preventive efficacy for aggressive or fatal prostate cancer, and there are no established biomarkers that can be used to do this. I have proposed that targeting recurrence of prostate cancer after surgery (or radiotherapy) may be one way to predict prevention of aggressive prostate cancer, because it targets recurring cancers, which by definition are aggressive and potentially fatal. However, when we tested whether soy protein consumption could prevent recurrence, we obtained a convincing null outcome (53), even though there is persuasive epidemiologic and preclinical evidence of preventive efficacy of soy (54–57). Studies of changes in PSA levels in patients with prostate cancer supplemented with soy were also essentially null (58).

There is only one published phase II presurgical study of selenium and vitamin E; gene expression changes were found in the prostate after 3 to 6 weeks of treatment with the same agents that were tested in SELECT (59). However, none of these changes have validated significance for prediction of the out-

come of SELECT. Presurgical treatment with the 5 α -reductase inhibitor finasteride induced apoptosis (23) but did not cause a reduction in proliferation index (24). Dutasteride also induced apoptosis (26, 28) but, surprisingly, increased the proliferation index (28); microvessel density was not consistently affected (26, 28). In addition, dutasteride suppressed staining for androgen receptor and the androgen-regulated TMPRSS2 gene product (25). Morphometric parameters were not consistently affected by 5 α -reductase inhibitors (24, 26–28). Thus, it appears that induction of prostatic epithelial apoptosis is potentially the most predictive intermediate marker of chemopreventive effects, but this remains to be validated and confirmed with other agents.

Why Are There Discrepancies between Epidemiologic and Preclinical Data and the Outcomes of Clinical Trials?

Several discrepancies, identified above, comparing the outcomes of RCTs and those of epidemiologic and preclinical studies are confusing, but there may be plausible explanations. Differences in timing of exposure may be particularly important. Epidemiologic studies and most animal experiments involved long-term (or even multigenerational) exposures, whereas the RCTs were conducted in men who probably already had small cancers in their prostates (60, 61). Perhaps only interventions starting early in life may have considerable preventive efficacy, particularly dietary changes, such as soy consumption, but it will be impossible to test these in RCTs.

The specific preclinical animal models used and the particular forms of agents applied in preclinical and clinical studies are probably critical factors as well. The MNU plus testosterone rat model may be driven by androgen more than prostate cancer in humans, whereas most of the mouse models are not androgen dependent (except when androgens are required to activate oncogenes or conditionally knocked out tumor suppressor genes). Flutamide, which was potently inhibitory in the MNU plus testosterone rat model, may have stronger antiandrogenic activity than the 5 α -reductase inhibitors that had only modest preventive activity in both a rat model (50) and human RCTs. Baseline status and form and dose of selenium and other dietary factors may also be critical determinants of chemopreventive efficacy (7, 62, 63). Of note, dose–response relationships may be nonlinear and U shaped, as has been suggested for selenium (63). These issues illustrate the complex nature of approaches to prostate cancer chemoprevention.

What Is Needed to Make Progress and Move Forward with Prostate Cancer Chemoprevention?

High-throughput systems to identify new candidate agents for prostate cancer chemoprevention need to be developed and validated. Once promising candidate agents have been identified, we need to apply a systematic approach to (i) carry out studies with the most promising and most relevant animal models of all agents already tested in phase II and III trials, including agents that were negative in RCTs; (ii) compare the animal study results with outcomes of clinical trials to validate the predictive value of the animal models and develop a database of these outcomes to identify the most predictive

preclinical model(s). Although this approach will be limited as only few agents have been tested in RCTs thus far and because of difficulties comparing agents that differ in mechanism of action, attempts should be made to conduct such comparisons going forward.

The same approach should be used to systematically compare the effects of candidate agents on intermediate biomarkers in phase II trials with cancer outcomes of phase II and III trials to identify the most predictive biomarkers and phase II trial designs. Phase II testing of agents that were negative in phase III studies to determine how to predict a negative outcome is, of course, not possible.

Only if we do all of the above suggested research, will there be a future for prostate cancer chemoprevention in my view. It seems at present that vitamin D and lycopene are less likely to be moved forward as prostate cancer chemoprevention agents (64–66), but vitamin D₃ and ω-3 fatty acids are being studied in a phase III study (VITAL; ref. 67) and should thus be tested now in preclinical models and, if possible, in small biomarker-based phase II trials before the VITAL study is completed; this will allow developing data that can be used to assess predictive value of preclinical studies and smaller clinical trials. Aspirin (68–70) and perhaps statins (71, 72) will possibly be tested in future phase III clinical trials. It is absolutely critical to first test these agents in multiple animal models and phase II studies with intermediate biomarker endpoints, before phase III RCTs are undertaken.

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Conclusions

Prostate cancer chemoprevention is both needed and possible, with a focus on preventing lethal cancers. Markers of fatal/lethal disease need to be identified for use as intermediate biomarkers in clinical trials. A rational systematic approach to identification of candidate agents for prostate cancer chemoprevention needs to be developed based, in part, on high-throughput screening and solid information on mechanisms of action and biology of candidate agents and potential molecular targets. A systematic evaluation of the predictive value of preclinical models, phase II trial designs, and intermediate biomarkers is urgently needed; induction of prostatic epithelial apoptosis is potentially the most predictive marker of chemopreventive effects. These research activities and evaluations are all needed to make real progress on prostate cancer chemoprevention. New phase III RCTs should be based on adequate phase II studies and results of solid preclinical research.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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