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POTENTIAL TARGET POPULATIONS AND CLINICAL MODELS FOR TESTING CHEMOPREVENTIVE AGENTS

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ABSTRACT

Target populations for chemoprevention trials should include those at higher than average risk for the development of prostate cancer as defined by explicit epidemiologic and genetic criteria. Such populations include a "primary prevention" group without histologic or clinical evidence of cancer, and several clinical models of "secondary prevention," including those with clinically evident disease prior to definitive therapy and those at high risk of recurrence after therapy based on histological or biochemical status. Each risk group and clinical model has potential advantages and disadvantages, and the mechanisms that underlie disease development and progression in each group may be unique. These observations give rise to many potential clinical trials of specific agents. These trials should also include collection of data on potentially confounding influences on disease development and progression. UROLOGY **57** (Suppl 4A): 171–173, 2001. © 2001, Elsevier Science Inc.

The identification and recruitment of high-risk study populations is necessary for the formulation and running of prostate cancer prevention trials. Specific clinical situations or models also need to be identified to allow explicit selection criteria and identify appropriate clinical and surrogate endpoints.[1] Based on the hypothesis that the specific molecular mechanisms that underlie the development or progression of disease in each risk group and model may be unique and that different agents may be useful for differing situations, it seems apparent that multiple potential chemopreventative agents should be tried in all risk groups and clinical models to best define which agents appear promising for large-scale studies.

POTENTIAL TARGET POPULATIONS FOR CHEMOPREVENTION

Target populations appropriate for study can be subdivided into those with low, intermediate, and high-risk of developing prostate cancer based on current epidemiologic evidence.[2–5] Subgroup stratification, advantages, and disadvantages of each target group are compiled in Table I. Several potential confounds in subgroup definitions are evident. For example, other than self-description, there is no clear agreement on what constitutes a specific racial group, and use of this definition could be confounded by lack of clear criteria for inclusion. Furthermore, emerging evidence suggests that specific genetic profiles that predispose to prostate cancer may be more prevalent within specific groups, further blurring the categorical distinctions.[6] Finally, histologic criteria for the definition of risk are prone to the vagaries associated with subjective interpretation of biopsy specimens and to sampling error.

CLINICAL MODELS

The testing of potentially active agents for the prevention of prostate cancer in clinical models of patients with active disease is also appropriate. Collectively these models of "secondary prevention" should be considered fertile ground for identifying promising agents that may have activity in true chemoprevention trials, although they may also yield useful information on the management of patients with disease in specific clinical situations. The molecular mechanisms that underlie disease progression are likely to be different for each model, and the results for a particular model may not be generalizable. The presurgical model allows for pre- and posttreatment tissue biopsies

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TABLE I. *Target populations*

Risk Group	Specific Population	Advantages	Disadvantages
Low	General population	• Easily definable • Readily available • Results widely applicable	• Rate of progression slow • Requires large study population and long follow-up interval • Studies costly
Intermediate	African Americans	• Higher risk than general population	• Difficult to define • Difficult to recruit because of perceived bias
	Genetic		
	Family history	• Double or greater the risk of prostate cancer	• Ascertainment bias • Risk varies with no. of affected family members, age of onset, and degree of relatedness • Likely to be genetically heterogeneous
	HPC-1 linked	• Genetically homogeneous	• Identification invasive and costly • Affected subjects rare
	Other genes	• Genetically homogeneous	• Identification invasive and costly • Affected subjects rare • Risk of progression undefined
High	High-grade PIN	• Highest known risk	• Sampling error • Diagnosis subjective • Uncommon

HPC = hereditary prostate cancer; PIN = prostatic intraepithelial neoplasia.

TABLE II. *Models of secondary prevention*

Model	Advantages	Disadvantages
Presurgical	• Early stage disease • Readily available study population • Pre- and posttreatment tissue available for biologic study	• Treatment period short
Elevated PSA/negative biopsy	• Well-defined histologic endpoint	• Risk of progression undefined • Sampling error
Adverse pathology after RP	• High risk of progression	• More advanced disease • Clinical endpoint
Rising PSA after RP or RT	• High risk of progression	• Most advanced disease • Clinical endpoint

PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiation therapy.

for molecular assessment of the tumor microenvironment as modulated by an agent, making it an attractive and potentially very powerful model system both for identifying a clinical effect and for the generation of new biological hypotheses. The other models rely only on clinical outcomes, such as PSA progression rates, about which there is more uncertainty and less agreement regarding their potential as useful endpoints.[7] The advantages and disadvantages of these models are listed in Table II.

IDENTIFICATION OF OTHER RISK GROUPS

Recognizing the limitations of current risk stratification, other additional risk groups can be defined (Table III). A useful adjunct would be the construction of a prostate-cancer-specific multifactorial Gail-like model as used in chemoprevention trials of breast cancer for prediction of individual risk.[8] If validated, such a model could reduce the number of subjects needed for a large-scale prevention trial while still generating results that are widely applicable to the general population. Accumulating evidence suggests both individual- and population-based variations in the metabolism of testosterone and other androgens necessary for the development of prostate cancer,[9,10] and it appears that simple biochemical tests could also be applied to individual subjects to define new risk groups. Other potential risk groups include genetically isolated populations with unique clinical

TABLE III. *Other risk groups*

- Multifactorial Gail-like model
- Variable metabolic phenotypes
- Genetically isolated populations
- Dietary and personal habits

TABLE IV. *Other data to be collected*

- Dietary habits
- Family history
- Genetic linkage
- Dietary supplements, vitamins, and micronutrients
- Nontraditional medicines

characteristics and risk groups based on dietary and other personal habits, recognizing that no or limited data currently exist to support the existence of these groups.

POTENTIAL CONFOUNDS BEARING ON THE RISK OF DEVELOPING PROSTATE CANCER

Finally, there are numerous observations in the epidemiologic literature suggesting associations between various dietary, lifestyle, genetic, and nontraditional factors and the risk of developing prostate cancer (Table IV).[11] It is recognized that it will not be practicable to quantify most of these factors in the conduct of a large-scale prevention trial, but it is recommended that data relevant to these factors be collected for secondary analysis and the analysis of potential confounds for unexpected results.

CONCLUSION

The identification of appropriate target populations is important for the development of small- and large-scale trials of primary and secondary chemoprevention. Each model has advantages and disadvantages for the design of clinical trials, and many different models should be employed to ensure adequate testing of molecular hypotheses for each stage of disease. Identification and characterization of genetic susceptibility loci will refine selection criteria for those at highest risk and with specific molecular targets. Potential confounding factors in the identification of target populations that may affect outcomes should be identified prior to trial design.

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