Genes Plus Family History Show Prostate Ca Risk

BY BRUCE JANCIN

DENVER — A man's absolute risk of developing prostate cancer over a 20-year period can be estimated by determining the number of risk alleles present on a simple genetic test and then taking family history into account.

It's known that an average 55-year-old man has a 13% risk of developing prostate cancer during the next 20 years. But by adding up how many of 14 known risk alleles the man has on single-nucleotide polymorphisms, his risk can be defined far more accurately.

For example, a man with seven or fewer of the risk alleles plus a negative family history has only an 8% absolute risk of being diagnosed with prostate cancer at age 55-74. The risk shoots up to 52% in a man with 14 risk alleles and a positive family history, Dr. Jianfeng Xu explained at the annual meeting of the American Association for Cancer Research.

This latter highest-risk group includes 8% of the general adult male population, noted Dr. Xu, professor of epidemiology and cancer biology at Wake Forest University, Winston-Salem, N.C.

He and his coworkers developed their risk model by studying 2,893 men with prostate cancer and 1,781 without the disease who had previously participated in a Swedish case-control study. The investigators found that while each of the risk alleles contributed a relatively small increase in risk, the risk was additive.

Moreover, the risk was further enhanced in a predictable way by the presence of a positive family history. For example, the 20-year absolute risk in a man with seven or fewer risk alleles and a negative family history is a mere 8%, but it rises to 17% with a positive family history. At the other extreme, a man possessing 14 risk alleles but a negative family history has a 24% risk of being diagnosed with prostate cancer at age 55-74; having a positive family history increases that risk to 52%.

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DR. XU

The investigators subsequently confirmed their findings in a retrospective analysis of data from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.

Dr. Xu conceded that the model has a major limitation: It doesn't distinguish between indolent and aggressive forms of prostate cancer. Thus, using the model would likely result in overtreatment of many men identified as being at high absolute risk, but who have indolent disease. The investigators have identified several single-nucleotide polymorphisms that appear to distinguish between nonaggressive and lethal prostate cancer, however, and are now doing confirmatory testing.

Even if these new candidate risk alleles don't pan out, Dr. Xu said he sees the current version of the absolute risk assessment as having potential utility. For example, men identified as high risk might elect to embark on a program of risk reduction through diet and lifestyle modification along with chemoprevention using finasteride, which has been shown to reduce prostate cancer risk by about 25%.

For men at average risk, finasteride could reduce their 20-year absolute risk from 13% to 10% at the cost of roughly $1.6 million per life-year gained. But for men at very high risk, the absolute risk reduction conferred by finasteride would be substantially greater and cost per life-year gained would be lower, Dr. Xu said.

He and his colleagues plan to launch a prospective prostate cancer prevention trial using risk alleles and family history to guide chemoprevention with finasteride.

"More replication is definitely needed before this is ready to go to the clinic, but this is taking us one step closer to the personalized medicine approach," observed Dr. Peter G. Shields of the department of medicine at Georgetown University Medical Center and deputy director of the Lombardi Comprehensive Cancer Center, Washington. ■