

Emerging Risk Factors for Urologic Diseases

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Modern medicine has brought us many miracle cures. In the 21st century, especially, we are blessed with increasingly powerful disease combating tools, such as functional genomics, proteomics and stem cells. Decades of medical and pharmaceutical research have produced thousands of medicines that allow us to treat and prevent diseases better than ever before. Furthermore, risk factors for many major diseases are being identified. To name a few, we now know that high cholesterol and chronic inflammation are two most prominent risk factors for cardiovascular diseases. We also know that obesity is one of the major contributing factors for type II diabetes. Cigarette smoking and air pollution are major environmental causes of respiratory diseases and lung cancers. Unfortunately, specific risk factors for many urologic diseases are yet to be identified. In this editorial, I will discuss emerging urologic risk factors based on recent research findings and their implications on what we should be looking ahead. Understanding risk factors is obviously important because it allows us to avoid disease development in the first place. Risk assessment facilitates clinical prognosis and understanding of disease development mechanisms.

Genetic Risk Factors

Urologic diseases encompass a wide variety of diseases that can be subdivided into three broad classes, 1) developmental abnormality such as hypospadias, 2) functional deficiency such as incontinence and male impotence, and 3) abnormal or cancerous growth in kidney, urethra, bladder, ovary, testis and prostate. Many of these diseases have underlying genetic bases. Traditionally, disease causing genes are identified by positional cloning of the inherited disease genes through family pedigrees. The bigger the family pedigrees are, the easier it is to identify the associated disease causing genes. The availability of large numbers of families with polycystic kidney diseases have allowed the identification of the PKD1 and PKD2 genes that account for majority cases of autosomal dominant polycystic kidney diseases [1, 2]. Pedigrees for nephronophthisis are generally smaller, however, causal genes have also been identified [3]. The success in these cases is largely due to clear-cut linkage of the diseases to germline mutations that can be repetitively identified in successive generations of the same family. However, many urologic disease conditions are caused by spontaneous mutations that occur in cells within the affected tissues in individual patients. These mutations also have tremendous values in diagnosis, prognosis and drug development, however, they are more difficult to identify.

Recently, scientists, with more advanced technology, have made encouraging success in identifying prevalent mutations in various forms of urologic cancers, many of which are caused by somatic mutations. For prostate cancers, international teams of researchers recently reported in February 2008 the findings obtained from comparing DNA from 24,500 prostate cancer patients with DNA from 37,800 men without prostate cancer [4–6]. These comparisons linked prostate cancer to at least 11 new genetic variations at the MSMB, LMTK2, KLK3, CTBP2, JAZF1, CPNE3, IL16, CDH13, EHBP1, NUDT10, and NUDT11 loci [4–6]. These new prostate cancer candidate genes differ from the popularly known tumor suppressor genes and oncogenes such as Rb and H-ras. Although it is too early to predict how these 11 genes function, they may have specific roles in prostate cancers as the MSMB gene makes a semen protein and the CTBP2 gene is highly active in prostate tissues [5]. Further analysis of these should shed lights on prostate cancer genetics.

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This study illustrates the power of modern whole genome scanning technology in searching for abnormal mutations responsible for urologic cancers without relaying on family pedigrees. Similar whole genome scanning approaches have been applied to endometrial cancers. Of the 187 endometrial cancer samples sequenced, researchers in May 21, 2007 identified alterations in FGFR2 in 12 percent of tumors that carried a constitutively activated form of FGFR2 [7]. FGFR2 encodes a receptor for FGF growth factor that plays critical role in cell growth and differentiation. This study adds FGFR2 to the previous list of MLH1 and MSH2, the two DNA mismatch repair genes that make a substantial contribution to endometrial and colon cancer incidences. For bladder cancers, deletion of a portion or all of chromosome 9 is a frequent somatic event [8]. It is reasonable to suspect that several genes on chromosome 9 that control cell growth and division such as FGFR3, HRAS, RB1, TP53, and TSC1 may contribute to bladder cancers, however, roles of other genes on chromosome 9 could not be easily ruled out.

One of the intriguing questions is whether and to what extent do urologic cancers share similar genetic risk factors with other types of cancers in our body? We have known for sometimes that hereditary nonpolyposis colorectal cancer (CRC) confers increased risk not only for colon cancer but also for cancers in the uterus, ovaries, renal pelvis and urethra. History of ovarian and endometrial cancer is associated with increased risk for CRC. Is there a general association between CRC and urologic cancers? In May 2008, researchers reported the first largest study involving 14 population-based cancer registries and data collected from 1973 to 2000 (14% of US population) [9]. This study showed that “the risk for CRC was increased among patients with previous ureteral cancer (SIR, 1.80; 95% confidence interval [CI], 1.46–2.20) and renal pelvis cancer (SIR, 1.44; 95% CI, 1.20–1.72). This risk was greatest among patients who received the diagnosis of renal pelvis or ureteral cancer before the age of 60 years. There was a minimal increased risk for subsequent CRC in patients with bladder or renal parenchymal cancer. Overall, the risk for urologic cancer was increased after a diagnosis of CRC (SIR, 1.24; 95% CI, 1.20–1.28), with the highest risk for subsequent renal pelvis and ureteral cancers in patients with a CRC diagnosis before the ages of 50 to 60 years or multiple primary CRCs” [9]. An exciting note from this is that it is possible to draw genetic risk factors for specific urologic

cancers from specific non-urologic cancers. This type of study is of great value as we look deep down into what constitutes various cancer genomes.

Technical advantage of studying cancers includes the ease to obtain sufficient cell mass for genetic analysis. This is not the case for many other urologic diseases. So, how close are we to understand genetic predisposition for complex urologic conditions such as urinary incontinence and male impotency? The answers to this question seem to largely depend on how physicians are willing to establish family pedigrees or patient DNA data bases. Family risks were present for two of the main types of incontinence, stress and urge incontinence. Statistics showed that daughters of mothers with urinary incontinence had a 1.3-fold increased risk of being incontinent themselves. It is conceivable that modern whole genome scanning technology would be able to eventually track down the culprit genes for complex urologic conditions. In February 14, 2008, researchers reported the first critical gene identified for pelvic organ prolapse (POP) which involves abnormal descent of pelvic organs that lead to urinary incontinence among other symptoms [10]. *Hoxa11* is a critical gene required for normal development and maintenance of uterosacral ligaments (USLs) that support the positioning of uterus and vagina. Mice lacking *Hoxa11* do not form USLs although this has yet to be confirmed in humans [10]. Interestingly, expression of *HOXA11* was markedly decreased in the USLs of women with POP, which coincides with decreased expression of type I and type III collagen and coordinated increase of expression of *Mmp2* that are known to mediate connection tissue functions [10]. It appears that this study has defined an important molecular pathway for maintaining mechanical strength of USLs that directly contributes to incontinence.

Environmental Risk Factors

Endocrine disruptors are synthetic chemicals that are “hormonally active agents” as recently defined by the U.S. National Academy of Sciences. These chemicals either mimic or disrupt hormone actions in our body by boosting or suppressing hormone production, altering hormone metabolism or directly affecting the processes controlled by hormones. Chemicals that are known human endocrine disruptors include diethylstilbesterol (DES), dioxin, polychlorinated biphenyls (PCBs), DDT, and many other pesticides.

Endocrine disruptors that have anti-androgenic or estrogenic properties are the most visible environmental risk factors for reproductive urologic diseases. This was shown first by numerous reproductive problems in wildlife such as fish and fish-eating birds in the Great Lakes areas, which are contaminated with PCBs and other man-made chemicals. As all vertebrates including humans are fundamentally similar in hormone regulated sexual development and function, endocrine disrupting agents are likely to have significant consequences in humans. This was inadvertently shown in the 1950s and 1960s when diethylstilbestrol (DES), a synthetic estrogen, was given to pregnant women to prevent miscarriages. Following this in 1971, high rates of unusual vaginal cancers were reported in teenage girls from mothers with known DES exposure during pregnancy. These girls also suffered birth defects in the uterus and ovaries [11].

Although the uses of DES and DDT are banned, the danger of endocrine disruptor exposure continues to exist. Many chemicals found in widely used plasticizers, insecticides, herbicides, fumigants and fungicides are suspected of being hormonally active albeit at low potency based on animal studies. Exposure to endocrine disruptors can occur through ingestion of these chemicals from everyday uses of plastic linings such as those in metal food cans and hospital intravenous bags. Many endocrine disruptors are stable in the environment and accumulate in fat tissues of livestock. Therefore, the greatest exposures come from eating contaminated fish or animal meat and greatest danger come from accumulative effects of these chemicals in our body. Chemicals commonly detected in people include Bisphenol A, Polybrominated diphenyl ethers, and a variety of Phthalates.

In recent May 2008 annual meeting of the American Urological Association, a study from Emory University School of Medicine reported higher incidences of congenital anomalies such as undescended testicles and hypospadias in toddler boys whose mothers had higher serum levels of organohalogens such as PCBs and DDT. This study and other studies in the Michigan area further confirm the long existing hypotheses that maternal exposure to endocrine disrupting chemicals contribute to urological anomalies. Based on what we know about the broad roles of hormones in human physiology, it would not be inconceivable that endocrine disrupting compounds could be the

culprit behind a diverse range of reproductive problems, including reduced fertility, male and female reproductive tract abnormalities and cancers, skewed male/female sex ratios, loss of fetus, menstrual problems, early puberty, and sexual behavior problems. Moreover, animal studies showed that *in utero* and neonatal DES exposure resulted in uterine abnormalities not only in daughter animals of the exposed mothers, but also surprisingly, in granddaughter generations of female animals that have not been directly exposed [12–14]. Therefore, we should be particularly paying attention to potential trans-generational effects of endocrine disruptors in humans as this suggests that environmental agents could bring long lasting, if not irreparable, damages in human health [15].

Other Emerging Risks We Should Be Looking For

Urologic diseases include developmental and functional deficiencies, fibrosis, abnormal cell proliferation and cancers. Each type of these diseases is likely to have specific genetic as well as environmental risk factors. Besides genetic and environmental risk factors, there seems to be a general risk from chronic inflammation in urologic organs as adverse consequences of sexually transmitted diseases or frequent urinary tract infections. Future work is required to establish causal relationship between specific infective agent and specific urologic ailment. Such effort is warranted as exemplified by the identification of human papillomavirus (HPV) as the infective agent for causing cervical cancer. The 2006 successful development and approved use of HPV vaccine Gardasil will quickly generating data on whether the vaccine is effective in curbing cervical cancer incidences vaccinated in women. While identifying infective agents is important, we should also address whether chronic inflammation itself directly contribute to the development or progression of urologic diseases. Chronic inflammation is recently recognized as a culprit for a large number of diseases such as heart disease, neurological degenerative disease, intestinal diseases and joint diseases [16–18].

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