DERLEME REVIEW

PENİS KANSERİ İÇİN RİSK FAKTÖRLERİ VE SÜNNET

CIRCUMCISION AND RISK FACTORS FOR PENILE CANCER

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ÖZET Penis kanseri batı ülkelerinin çoğunda diğer ülkelere göre daha nadir görülür. Penis kanseri tanısı erken dönemde gözlenen ve semptoma yol açmayan lezyonların hastalar tarafından fazla önemsenmemesi ve dikakate alınmaması nedeniyle gecikebilir. Penis kanseri olgularının büyük çoğunluğu skuamöz hücreli kanserdir. Bazı risk faktörleri tanımlanmış olsa da penis kanserinin kesin sebebi tam olarak anlaşılabilmiş değildir. Fimozis penis kanserinin gelişiminde rol aldığı düşünülen konular içinde en fazla bahsi geçen durumlardan biridir. Yapılan bilimsel çalışmaların çoğundan elde edilen sonuçlar yenidoğan veya çocukluk çağında sünnet yapılması ile riskin azalması arasında anlamlı bir ilişki olduğunu göstermektedir. Yine yapılan çalışmaların çoğundaki sonuçlar, çocukluk çağında yapılan sünnetin koruyucu etkisinin fimozis ve balanitis gibi kötü genital hijyen ile ilgili inflamatuvar durumların ortadan kaldırılmasına bağlı olduğunu vurgulamaktadır. Sünnet olmamış kişilerde eğer genital bölge hijyeni kötü ise fimozis olmasa da bu bölgede mikroorganizmalar ve smegma birikimi meydana gelebilir. Birçok çalışmada sigara içiciliğinin de penil skuamöz hücreli kanser riskinde artış ile ilşkili olduğu sonucu elde edilmiştir. İster tedavi amaçlı olsun ister estetik amaçlı olsun ultraviyole radyasyona maruz kalmak da farklı derecelerde penil skuamöz hücreli kanser riskini artırabilir. Kronik irritasyon ve penil travma, kötü genital hijyenle eş zamanlı olarak uzun süreli olarak kimyasal bileşenlere maruz kalmak da penis kanserleri ile ilişkili durumlar olarak yapılan çalışmalarda bildirilmiştir.

Anahtar Kelimeler: Penil tümörler; Sünnet; Fimozis

ABSTRACT: Penile carcinoma is relatively uncommon in most Western countries. The diagnosis of penil cancer may be delayed because many patients disregard early asymptomatic lesions. Majority of the cases are squamous cell carcinoma (SCC). Although several risk factors commonly are recognized, the exact cause of penis cancer is not definitely known. Phimosis is one of the most mentioned cause in the pathogenesis of penile SCC. Studies have consistently reported neonatal or childhood circumcision to be associated with reduced risk, which corresponds geographically with reduced rates of penile SCC in populations practicing neonatal circumcision. The protective effect of childhood circumcision seems to be attributable to the elimination of inflammatory conditions related to poor genital hygiene, such as phimosis and balanitis. Accordingly, an intact foreskin has been shown not to be associated with increased penile SCC risk in the absence of phimosis. Poor genital hygiene in uncircumcised men, even in the absence of phimosis, may also lead to the retention of microorganisms and secretions, including smegma. Tobacco smoking, particularly current smoking, has been reported in a number of studies to be linked to increased risk of penile SCC. Ultraviolet radiation exposure, either therapeutic or recreational, may increase the risk of penile SCC. Human papillomavirus has been implicated as a causal agent in penile cancer, suggesting that this cancer may be a sexually transmitted disease. Chronic irritation or trauma and prolonged exposure to chemical compounds together with poor hygiene have been reported in association with penile SCC.

Key words: Penile Neoplasms; Circumcision; Phimosis

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Penile carcinoma is relatively uncommon in most Western countries.[1] The diagnosis of penil cancer may be delayed because many patients disregard early asymptomatic lesions. Penile cancer is, in the majority of cases, of squamous epithelial origin (squamous cell carcinoma [SCC]) and approximately half of the tumors are in situ (45%) and half are invasive (55%). In the Western world, SCC of the penis is a rare malignancy occurring mainly among elderly men above age 60 years and with a standardized annual incidence of <2 per 100,000 men.[2-5] In the United States, penile cancer accounts for 0.3% to 0.6% of all cancers in men and 2% of male genital cancers, with mortality of <1% to 2%.[6-7] The incidence is considerably higher, 10% to 20%, in some African, Asian, and South American countries, including Uganda, China, and India.[6,8-11] Incidence may also differ among people who belong to the same ethnic group but who live in or move to different geographic areas, but whether these differences are related to social factors (poor living conditions) or to environmental factors (hot, humid climates) is unclear.[12-13] In some instances, striking differences among different populations who live in the same geographic area, such as India or Indonesia, strictly depend on a varied cultural and religious background, since penile cancer is rare among those religious communities in which circumcision is practiced during the neonatal or prepubertal age, such as Muslims, Jews, and the Ibos of Nigeria, compared with those in which circumcision is not routinely performed, such as the Hindu.[14-16]

Although several risk factors commonly are recognized, the exact cause of penis cancer is not definitely known. Daling et al.[5] reported that 3 risk factors were more important in the development of invasive than in situ penile cancer: a history of phimosis, lack of circumcision in childhood, and cigarette smoking. Phimosis is one of the most mentioned cause in the pathogenesis of penile SCC. It is frequently caused by collection of smegma that leads to inflammation and chronic irritation of the foreskin, with narrowing of the preputial sac and adhesions between glans and prepuce. Lack of personal hygiene may worsen the condition. Phimosis induces histologic changes in the epithelium of the preputial sac.[17] Experimental studies in rabbits have shown that artificially induced phimosis and scarification are necessary to induce tumor formation after topical application of a chemical carcinogen.[18] Studies have consistently reported neonatal or childhood circumcision to be associated with reduced risk, which corresponds geographically with reduced rates of penile SCC in populations practicing neonatal circumcision.[5,19-23] The protective effect of childhood circumcision seems to be attributable to the elimination of inflammatory conditions related to poor genital hygiene, such as phimosis and balanitis. Accordingly, an intact foreskin has been shown not to be associated with increased penile SCC risk in the absence of phimosis.[3-5,20-21,24-28] Poor genital hygiene in uncircumcised men, even in the absence of phimosis, may also lead to the retention of microorganisms and secretions, including smegma.[18] A high incidence of penile SCC is found in developing countries, such as Sri Lanka, Thailand, China, Latin America, and East Africa, where routine genital hygiene is a problem because many homes do not have running water. Low incidences are reported in Western countries (United States, Great Britain, and Sweden) with a high standard of sexual hygiene.[12] In Uganda, the incidence of penile SCC is lower in those tribes who have good hygienic habits, although they do not routinely practice circumcision.[29] Smegma derives from desquamation of epithelial cells in the preputial sac and it begins to form during the first days of life. *Mycobacterium smegmatis* converts the smegma sterols into carcinogenic compounds.[18,30] The carcinogenic action of retained smegma has been proved in animals.[31] Experiments on mice have demonstrated the induction of an SCC by transferring human smegma into the cervix.[32-33] In horses, SCC of the penis occurs 10 times less frequently in stallions than in geldings, in whom the lack of erections implies a reduction of cleaning of the preputial sac.[34]

Tobacco smoking, particularly current smoking, has been reported in a number of studies to be linked to increased risk of penile SCC.[5,20,26,35] For instance, current smokers were at double risk of penile SCC compared with lifelong nonsmokers in the Seattle-based case-control study.[5] However, not all studies are in support of tobacco smoking as an important etiologic factor. A case-control study in China failed to find support for a causal role of tobacco smoking, and researchers in Sweden reported only a weak, positive association with current consumption of >10

cigarettes per day.[26,36] Ultraviolet radiation exposure, either therapeutic (psoralen plus ultraviolet A; ultraviolet B) or recreational, may increase the risk of penile SCC to a different degree, depending on genetic background and treatment schedules, lower daily doses being more carcinogenic than higher daily doses with rest periods.[15,34,37,38] A 12-year follow-up study of 892 men in a cohort of patients who had been treated with oral methoxsalen (8-methoxypsoralen) and ultraviolet A photochemotherapy, reported a relative risk for penis cancer 286 times that of the general population. A 5-fold increased risk with ultraviolet B exposure was also detected.[39] For this reason, men who undergo ultraviolet exposure should have genital areas shielded.[15]

The importance of sexual behavior in the development of penile cancer remains unclear. Human papillomavirus (HPV) has been implicated as a causal agent in penile cancer, suggesting that this cancer may be a sexually transmitted disease.[40-41] HPV DNA sequences have been isolated from dysplastic lesions and carcinomas of the cervix and in carcinoma in situ and SCC of the penis.[42-43] In human beings, HPV 6 and 11 are seldom found in penile benign lesions, whereas HPV 16 and 18 are often isolated in invasive and in situ carcinomas.[42,44-45] HPV sequences have also been found in local and distant metastases of penile SCC.[46] Therefore HPV types have different biologic behaviors, which result in a variable clinical evolution and prognosis.[47] The oncogenic properties of some HPVs depend on the presence, in their genome, of transforming genes located in the E6 and E7 regions, which codify oncoproteins inducing proliferation and immortalization of keratinocytes by interaction with p53 and p105RB proteins.[42,48-50] HPV infection alone is probably not sufficient to induce a carcinoma in an immunocompetent host. Chemical and physical factors affecting host cell genes in viral genome-carrying cells should play an important role in determining the actual risk of cancer development. This conclusion is suggested by the spontaneous regression of many HPV-induced warts and by the long time between initial infection and eventual malignant conversion.[51] Studies performed on the sexual partners of women with severe intraepithelial cervical neoplasia or cervical carcinoma have found an incidence of 32.8% of malignant or premalignant penile HPV lesions.[52] There is no uniform agreement, however, about this correlation. Penile SCC has been observed in HIV-positive men and in transplant recipients, who carry a 36-fold increase of the risk of cancer development at any site, although the AIDS epidemic has not led to an increased incidence of penile carcinoma in areas such as Uganda, where HIV infection is widespread.[53-55] However, there has been a significantly increased incidence of verrucous carcinoma among HIV patients, and immune suppression is considered a relevant predisposing factor to carcinoma.[56]

Prolonged exposure to chemical compounds together with poor hygiene have been reported in association with penile SCC. Penile SCC has been reported in a farmer who claimed to be frequently exposed to different chemicals (insecticides and fertilizers, styrene, acrylonitrile) without practicing thorough hand washing. Penile SCC has also been reported in a Japanese man, circumcised in adulthood, who implanted two beads made from a plastic tooth-brush in the lateral aspect of the penis to increase coital excitation of his mate. It is not clear whether the SCC was caused by the chemical carcinogens (styrene, acrylonitrile), or the chronic irritation induced by the foreign body, or both.[57-58] Chronic irritation or trauma may be important in the etiology of penile cancer. The association of pre-existing scars, burned areas, and draining sinuses with the subsequent development of squamous cell carcinoma in other parts of the body is well established.[59-60] In the study by Madsen at al.[2] a history of penile trauma was not reported more frequently by penile SCC patients than controls. This is in contrast to findings in a case-control study in Western Washington/British Columbia, where researchers reported statistically significant ORs of 3.2 (95% CI, 1.5-6.8) and 5.2 (95% CI, 3.1-8.7) for penile injury and penile tear, respectively.[5] The reason for this difference between studies is unclear.

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