We read with interest the recent study by Chaturvedi et al. (1) concerning the risk of second cancers in a large number of survivors of cervical cancer. The authors of this well-designed and well-conducted study assessed the risk of second cancers that are known to be associated with human papillomavirus (HPV) infection and tobacco use in a cohort of 104,760 women (1). During a follow-up period that spanned more than 40 years, they found 12,496 incident cancers, 11,720 of which were solid cancers. Among the patients with solid cancers, there were 949 urinary bladder cancer patients (8%), and 536 of these underwent radiotherapy and 109 did not. The authors reported an overall standardized incidence ratio (SIR) for urinary bladder cancer of 3.44 among all cervical cancer patients (1). Chaturvedi et al. (1) divided the secondary cancers into HPV and smoking-related cancers and considered bladder cancers to be smoking related.

We pose some questions based on these data to highlight the fact that HPV is a new challenge for urological research. First, what is the potential role of HPV in bladder cancer development? Among 949 bladder cancer cases, 109 had not undergone radiotherapy, suggesting that the impact of radiotherapy on secondary bladder cancer development is low, even if Chaturvedi et al. (1) reported SIRs of 3.51 and 1.93 for patients treated and not treated with radiotherapy, respectively. Furthermore, of the 109 patients affected by secondary bladder cancers who had not undergone radiotherapy, how many smoked? As previously suggested by others, the probable role of HPV in the development of bladder cancer should be considered (2–4). Chaturvedi et al. (1) highlighted the fact that the effects of radiation, HPV, and smoking may interact through common cellular pathways such as the p53 tumor suppressor pathway. In fact, the evidence that HPV interacts with p53 pathway, through E6 protein expression to produce an oncological disease after a long latency time is well established in the current literature (5). The authors also reported that among women who did not receive radiotherapy, statistically significantly elevated SIRs were observed in the period beyond 40 years of follow-up only for cancers of the urinary bladder (1). This raises the question as to whether the reported secondary bladder cancer cases are due to the fact that HPV infection causes cervical cancer and then, after a subsequent latency time, causes bladder cancer. Finally, we would like to highlight the fact that the difficulty in establishing the true association between HPV and bladder cancer is due to inadequacies of the microbiological methods used for HPV diagnosis, as suggested by Tekin et al. (6).

**Response**

We thank Cai et al. for their interest in our study describing the long-term risk of second cancers among cervical cancer survivors (1). In our study, we assessed second cancer risk among 104,760 cervical cancer survivors in Denmark, Finland, Norway, Sweden, and, based on data from the Surveillance, Epidemiology, and End Results program, the United States. Compared with women in the general population, we observed statistically significant increased risks of urinary bladder cancer among cervical cancer survivors who initially received radiotherapy (536 bladder cancers among 52,613 women; standardized incidence ratio [SIR] = 3.51; 95% confidence interval [CI] = 3.22 to 3.83) and among women who did not receive radiotherapy initially (109 cancers among 27,382 women; SIR = 1.93; 95% CI = 1.59 to 2.34) (1).

Cai et al. raise the following questions: 1) whether the increased urinary bladder cancer risk among cervical cancer survivors, particularly among women who did not receive radiotherapy, could be due to an etiologic role for human papillomavirus (HPV) infection in bladder cancer and 2) what proportion of the 109 bladder cancer cases who did not receive radiotherapy were smokers. We did not have information regarding noncervical HPV infections or cigarette smoking in our study (1), thus precluding any assessment of the contribution of either HPV infection or cigarette smoking to the increased bladder cancer risk among women who did not receive radiotherapy.

Although we did not have information on smoking behaviors, it is well established that cigarette smoking is etiologically related to both cervical cancer and bladder cancer, with approximately twofold to threefold increased risks for each cancer among smokers as compared with nonsmokers (2). Thus, the elevated risk for bladder cancer among survivors who did not receive radiotherapy may, in part, be due to a high prevalence of smoking. Increased bladder cancer risk among survivors who did not receive radiotherapy could have also arisen from misclassification of radiation treatment. Although treatment misclassification among cervical cancer patients is low (3), it is possible that some women classified as not receiving radiotherapy may have actually received radiotherapy, as indicated by their
increasing bladder cancer risk over follow-up time (1), a pattern that is consistent with the late effects of radiotherapy.

Cai et al. suggest a model wherein HPV infection causes cervical cancer and then, after a subsequent latency, causes bladder cancer. HPV has been implicated in the etiology of primary urinary bladder cancers (4,5). Benign HPV-related condylomas, although rare, are known to occur in the bladder, indicating that HPV infection of the bladder is plausible (4). Further, HPV DNA has been detected in both transitional cell carcinomas and squamous cell carcinomas of the bladder (4). However, results have been inconsistent across studies, with HPV DNA prevalence in bladder cancer tissues varying from 0% to 80% (4,5).

Gillison and Shah (4) recently reviewed criteria to evaluate the plausibility of a HPV etiology for noncervical cancers, including epidemiological and virological characteristics such as increased incidence of the cancer under question among populations with high-risk sexual behavior and immunosuppressed populations, expression of viral oncogenes in the tumors, and the presence of serum antibodies to HPV oncogenes (E6 and E7) (4). Although bladder cancer has been associated with a history of sexually transmitted diseases such as gonorrhea, this is believed to be due to urinary tract inflammation and/or urinary stasis, rather than increased HPV infections (6). Bladder cancer incidence is not increased in immunosuppressed HIV-infected individuals (7). Finally, no studies have evaluated either HPV oncogene expression in tumors or the presence of HPV E6 and E7 serum antibodies among bladder cancer patients. Thus, we believe that there is currently insufficient evidence in the literature to link HPV infection with urinary bladder cancer, either among cervical cancer survivors or in the general population.

References


Notes

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