RESEARCH ARTICLE

Chronic Infections of the Urinary Tract and Bladder Cancer Risk: a Systematic Review

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Abstract

Literature on the relationship between recurrent urinary tract infections and urinary bladder carcinoma risk has been inconsistent. Therefore, we carried out this systematic review of observational studies to ascertain if there is any association between chronic urinary tract infection and urinary bladder carcinoma. A total of 10 databases were searched using Boolean: CINAHL, PUBMED, Google Scholar, Medline, Science Direct, SCIRUS, Cochrane, UK PubMed central, NHS evidence and WHO-website. The search yielded an initial hit of 3,518 articles and after screening and critical appraisal, seven studies were included for this review. Four articles reported an association between chronic urinary tract infections and bladder cancer while three concluded a weak or no association at least in one gender. Main findings in this review were that most of the studies reported an association between chronic urinary tract infections and bladder cancer risk. However, inferences about the causal association between chronic urinary tract infections and bladder cancer risk should be drawn cautiously considering the methodological limitations of case-control studies included in this review. Therefore, more empirical evidence is needed to determine the causal nature of relationships between chronic urinary tract infections and bladder cancer risk..

Keywords: Bladder cancer - chronic urinary tract infection - risk factor

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Introduction

Globally, bladder cancer incidence ranks 9th most common cancer and 13th most cause of mortality. (Parkin, 2008). Bladder cancer has the highest treatment cost compared to all other forms of cancer because of its reoccurrence and on-going monitoring requirements (Sievert et al., 2009). Epidemiological studies have yielded inconsistent results regarding bacterial infections of the urinary tract as a risk factor for transitional cell carcinoma of the bladder (Pelucchi et al., 2006; Abol-Enein, 2008). Therefore this systematic review of observational epidemiologic studies was conducted to appraise the existing account on relationship between chronic infections of urinary tract and bladder cancer.

Materials and Methods

A total of 10 databases were searched for publications on chronic and/ recurrent urinary tract bacterial infections and bladder cancer using Boolean search. The databases searched included Cochrane, CINAHL, PubMed, UK PubMed central, MEDLINE, SCIRUS, Science Direct, NHS-evidence, WHO website and Google Scholar. Key words used in Boolean search included bladder OR urinary bladder OR transitional cells OR squamous cell, cancer OR carcinoma OR tumour, chronic OR recurrent OR persistent OR continuous OR long duration OR frequent. Infection OR disease OR bacterial urinary tract infection OR lower urinary tract OR cystitis, 1 AND 2 AND 3 AND 4 AND 5. Our search included all the studies published between 1990 and 2012 and the initial hit yielded 3518 articles. After relevant screening by title, excluding duplication and by exclusion/inclusion criteria the total number of studies was reduced to 8 articles. Furthermore, these studies were screened based on quality appraisal tool (Effective Public Health Practice Project tool) and a total number of 7 papers were left for data extraction/ synthesis (Figure 1).

Results

Review of evidence on the relationship between chronic urinary tract infections and bladder cancer based on the results of seven selected articles revealed somewhat contrasting results, which are summarized as follow: A strong association between chronic urinary tract infections and bladder cancer was observed. In fact, bladder cancer

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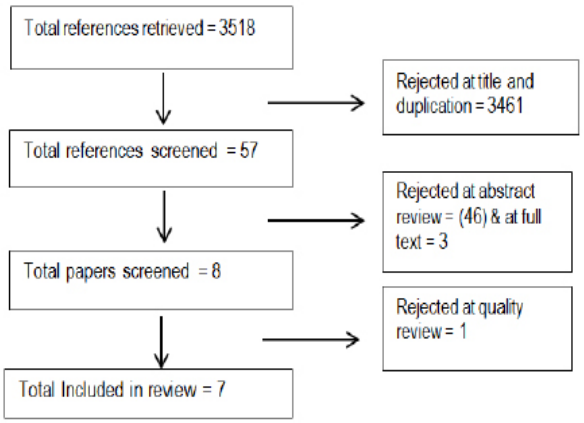

Figure1. Flow chart depicting the search and selection of the articles for review

Figure 1. Flow Chart Depicting the Search and Selection of the Articles for the Review

risk tended to increase with increasing number of urinary tract infections episodes (relative risk (RR) = 5.0 for ≥ 4 episodes, *P*trend < 0.001) (La Vecchia et al., 1991). Another study documented that recurrent urinary tract infections for three or more times significantly increased the risk of transitional cell carcinoma of bladder (aRR = 2.6; 95%CI: 1-7-3.9) (Sturgeon et al., 1994). Furthermore, diagnosis of urinary tract infections at index visit showed significantly increased risk of bladder cancer (aRR = 3.0; 95% CI: 2.0 - 4.4) (Chow et al., 1997). Additionally, a significantly strong relationship of recurrent urinary tract infections with substantially increased bladder cancer risk (adjusted odds ratio (aOR) = 5.2; 95% confidence interval (CI): 3.7 - 7.4) was recoded in Iran (Shakhssalim et al., 2010).

On the contrary, it has been suggested that the history of cystitis was associated with significantly increased bladder cancer risk (aOR =1.5; 95%CI: 1.1 - 2.1) but the risk was weakened for infections diagnosed more than 1 year from the point of bladder cancer diagnosis. Furthermore, history of recurrent kidney infections turned out to be protective against bladder cancer risk (aOR= 0.2; 95% CI =0.04 -0.69)(Jhamb et al., 2007). Additionally, an increased risk of bladder cancer with infections starting ≤ 4 years before diagnosis (aOR = 15.00; 95% CL; 6.1-51.7) was recorded but no significant increased risk was observed for infections starting ≥ 5years before diagnosis of bladder cancer (OR = 1.44; 95% CI: 0.86-2.47). Further, it has been argued that the association between urinary tract infections and bladder cancer is possibly non-causal and more likely to be the consequences of cancer (Gonzalez et al., 1991). In agreement with above reports, it has been shown that history of bladder infections was associated with reduced bladder cancer risk among women (aOR = 0.66; 95% CI: 0.46 - 0.96), rather a greater reduction of bladder cancer risk was noted among women with multiple infections (aOR = 0.37; 95% CI: 0.18 - 0.78). However, this association of urinary tract infections with bladder cancer risk did not hold among men reportedly due to the limited study power (Jiang et al., 2009).

Discussion

Bladder cancer is a common malignancy, worldwide. It is the seventh most prevalent cancer, accounting for 3.2% of all malignancies [1]. The main finding of this review is that most of the studies reported strong association between chronic urinary tract infections and the risk of bladder cancer. Whereas only few reported either weak or no association at least in one of the gender. In addition to smoking, occupational exposures, nitrate contamination of drinking water with nitrate, urinary lithiasis, pelvic radiation and urinary tract infections including bacterial, parasitic, fungal, and viral infections have been implicated in the occurrence and progression of bladder cancer (Parkin, 2008; Pasin et al., 2008). Bacteria are the primary cause of urinary tract infections, with the vast majority (70-80%) attributed specifically to infection with Escherichia coli. Furthermore, the findings of an experimental study suggested that urinary bladder infection with Escherichia coli may play a major additive and synergistic role during bladder carcinogenesis (El-Mosalamy et al., 2012). Recently, recurrent urinary tract infection has been shown to be positively associated with increased bladder carcinoma risk in Netherland (Vermeulen et al., 2015). A recurring bacterial infection of urinary tract results in chronic inflammation that may lead to carcinogenesis (Lax and Thomas, 2002; Karin and Greten, 2005). One of the key molecules that link chronic inflammation and cancer is represented by the NF-ϰB family of transcription factors (Karin and Greten, 2005). It has been argued, once chronic inflammation of urinary bladder initiated by infectious organisms, it can mediate bladder cancer pathogenesis by stimulating cancer cell growth, invasion and metastasis through the recruitment of inflammatory cells and signaling molecules (Nesi et al., 2015). Chronic inflammation of the bladder may increase absorption of the carcinogens. Also, bacterial flora in the urine may contribute to the production of nitrites that are converted to carcinogenic nitrosamines (Hicks et al., 1977; Johansson and Wahlqvist, 1977; Radomski et al., 1978). However, it may be that urinary tract infections of bladder may represent a complication of cancer during its early growth before clinical diagnosis (Kantor et al., 1984).

In summary the results of some studies included in this review revealed a positive and strong association between urinary tract infections and bladder cancer. However, few studies showed a weak to no association between urinary tract infections. Regardless of these findings, all the studies included in this review used observational study design, which limits the ability of the researchers to determine if the association between chronic urinary tract infections and bladder cancer is causal. Therefore, further studies are indicated to examine the role of urinary tract infections in causation of bladder cancer.

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