Available online at www.sciencedirect.com
SCIENCE DIRECT®
Int. J. Hyg. Environ.-Health 208 (2005) 321–327
International Journal of Hygiene and Environmental Health
www.elsevier.de/ijheh

Methylenetetrahydrofolate reductase (MTHFR) variants and bladder cancer: A population-based case-control study

Margaret R. Karagas[a], Sunyeong Park[b], Heather H. Nelson[c], Angeline S. Andrew[a], Leila Mott[a], Alan Schned[d], Karl T. Kelsey[b,*]

[a]*Department of Community and Family Medicine, Dartmouth Medical School, Lebanon, NH, USA*
[b]*Department of Genetics and Complex Diseases, Harvard School of Public Health, Boston, MA, USA*
[c]*Department of Environmental Health, Harvard School of Public Health, Boston, MA, USA*
[d]*Department of Pathology, Dartmouth Medical School, Lebanon, NH, USA*

Received 8 November 2004; received in revised form 16 April 2005; accepted 17 April 2005

Abstract

Functional variants in the methylenetetrahydrofolate reductase (*MTHFR*) gene, including the 677C>T and 1298A>C polymorphisms, have been associated with a moderately reduced risk of several cancers, including colorectal cancers. While recent studies have investigated the role of these polymorphisms on bladder cancer susceptibility, results have been mixed. To clarify the role of *MTHFR* polymorphisms on bladder cancer risk, we genotyped *MTHFR* 677C>T and *MTHFR* 1298A>C in a population-based study of bladder cancer of 352 patients and 551 controls from New Hampshire, USA. The allelic frequency was 35.6% for *MTHFR* 677C>T and 40.4% for *MTHFR* 1298A>C among controls. We found no evidence of a main gene effect for either polymorphism (adjusted OR for *MTHFR* 677C>T variants versus the reference genotype = 1.1; 95% CI, 0.8–1.4 and adjusted OR for *MTHFR* 1298A>C variants versus the reference genotype = 1.0; 95% CI, 0.7–1.4). Odds ratios did not appear to differ by smoking status or gender. We observed differences in the risk estimates for the *MTHFR* polymorphisms by arsenic exposure, but they were not statistically significant ($P = 0.67$ for *MTHFR* 677C>T and $P = 0.12$ for *MTHFR* 1298A>C). Thus, our findings do not support the presence of a main gene effect. The possibility that *MTHFR* polymorphism affects susceptibility to environmental exposures warrants further consideration.
© 2005 Elsevier GmbH. All rights reserved.

Keywords: Bladder cancer; Case-control study; Gene–environment interaction; Arsenic; Smoking; Methylenetetrahydrofolate reductase polymorphisms

Introduction

Polymorphisms in the methylenetetrahydrofolate reductase (*MTHFR*) gene are receiving increasing attention as variants that may potentially influence methyl group metabolism and, thereby, alter chromosome integrity. *MTHFR* acts enzymatically to convert 5,10-

*Corresponding author. Tel.: +1 617 432 3313; fax: +1 617 432 0107.
E-mail address: kelsey@hsph.harvard.edu (K.T. Kelsey).

1438-4639/$ - see front matter © 2005 Elsevier GmbH. All rights reserved.
doi:10.1016/j.ijheh.2005.04.005

methylenetetrahydrofolate (which acts as the methyl donor in deoxythymidine monophosphate (dTMP) synthesis) to 5-methyltetrahydrofolate, the primary methyl donor for converting homocysteine to methionine. A common 677C>T variant (an alanine to valine change) within the N-terminal catalytic domain results in a thermolabile enzyme with reduced activity (35–50% of control values) (Frosst et al., 1995). A second 1298A>C variant (resulting in a glutamate to alanine substitution) within the C-terminal regulatory domain has been associated with decreased enzyme activity (Weisberg et al., 1998). Interaction between these two polymorphisms on enzyme function also has been reported (Feix et al., 2001; Fodinger et al., 2000, 2001; Skibola, 1999; van der Put et al., 1998; Weisberg et al., 1998).

Folate deficiency is associated with DNA strand breakage and uracil misincorporation into DNA (Duthie et al., 2002). Thus, if *MTHFR* polymorphic variants reduce folate levels by diminishing enzymatic activity, they could enhance the propensity for DNA strand breakage and cancer occurrence (Bailey, 2003). Alternatively, variant *MTHFR* activity could influence the availability of methyl donors by altering *S*-adenosylmethionine levels, and potentially, the methylation status of key tumor suppressor or promoter genes involved in bladder carcinogenesis (Duthie et al., 2000; Pogribny et al., 1997). Further, functional polymorphisms in *MTHFR* could affect the metabolism of other carcinogenic substances that undergo one carbon metabolism such as arsenic (McDorman et al., 2002; Spiegelstein et al., 2003).

To date, several studies have investigated the potential role of *MTHFR* polymorphisms on cancer susceptibility, particularly in colorectal neoplasia for which the *MTHFR* 677C>T and 1298A>C variants appear to moderately reduce risk (Sharp and Little, 2004). A number of recent studies have evaluated bladder cancer risk but with mixed results. An initial cohort study suggested a 5.5 fold risk of bladder and kidney cancer combined among 677C>T variant homozygotes (Heijmans et al., 2003). In contrast, three bladder cancer case-control studies found no overall association with *MTHFR* 677C>T genotype (Kimura et al., 2001; Lin et al., 2004; Sanyal et al., 2004), two found no association with the 1298A>C genotype (Lin et al., 2004; Moore et al., 2004), one study observed a reduced risk among heterozygotes for *MTHFR* 677C>T (Moore et al., 2004). However, most of these studies either did not have sufficient statistical power to detect gene–gene or gene–environment interactions or did not collect cofactor (e.g., smoking history) information. In the largest case-control study conducted to date, the variant allele of both polymorphisms was associated with an increased bladder cancer risk specifically among smokers (Lin et al., 2004). We evaluated the hypothesis that *MTHFR* polymorphisms may affect the risk of bladder cancer in a population-based study of bladder cancer from New Hampshire, USA.

Materials and methods

Study group

A detailed description of the study population has been published previously (Karagas et al., 1998). Briefly, the study includes incident cases of bladder cancer diagnosed from July 1, 1994 through June 30, 1998 from the New Hampshire State Cancer Registry. Controls were selected from drivers' license records (for those with age less than 65) and from Medicare enrollment files (for those with age greater than 65). We shared a control group with a study of non-melanoma skin cancer covering a diagnostic period of July 1, 1995 to June 30, 1998 (Karagas et al., 1998). We selected additional controls for bladder cancer cases diagnosed between July 1, 1995 and June 30, 1998 frequency matched to cases on age (25–34, 35–44, 45–54, 55–64, 65–69, 70–74 years) and gender.

Data and specimen collection

Trained interviewers administered a questionnaire to gather information regarding family history of cancer, socioeconomic status, and lifestyle factors such as cigarette smoking history and alcohol use. We collected and analyzed a toenail clipping sample for trace elements including arsenic using instrumental neutron activation analysis (Karagas et al., 2004). Arsenic accumulates in hair and nail tissue due to its affinity for sulfhydryl groups in keratin, and with proper treatment nails are not susceptible to external contamination (Agahian et al., 1990; Karagas et al., 2004). Levels reflect exposure to arsenic from airborne, water and food sources (ATSDR, 1999), and are reliable over a period of several years (Garland et al., 1993; Karagas et al., 2004).

A total of 459 bladder cancer patients and 665 controls were interviewed; this was 85% of cases and 70% of controls confirmed to be eligible for the study. Eleven cases were deemed non-cancerous upon histopathology re-review by the study pathologist and excluded from the analysis. Of the remaining cases, blood samples were available on 355 (79%) cases. A total of 559 (84%) controls provided a blood sample, 462 (86%) of which were shared with the skin cancer study. *MTHFR* genotyping was performed using a modified method of Skibola (Skibola et al., 1999a, b). Briefly, the primers used for *MTHFR* 677C>T were 5′TGAAGGAGAAGGTGTCTGCGGGA-3′ and

Download English Version:

https://daneshyari.com/en/article/9925384

Download Persian Version:

https://daneshyari.com/article/9925384

Daneshyari.com