Braz J Otorhinolaryngol. 2016;82(5):558–566

Brazilian Journal of
OTORHINOLARYNGOLOGY
www.bjorl.org

ORIGINAL ARTICLE

Polymorphisms in methylenetetrahydrofolate reductase and cystathionine beta-synthase in oral cancer – a case–control study in southeastern Brazilians☆

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Received 1 April 2015; accepted 2 October 2015
Available online 17 December 2015

KEYWORDS
Oral squamous cell carcinoma;
Methylenetetrahydrofolate reductase;
Cystathionine beta-synthase;
Genetic polymorphism

Abstract
Introduction: Oral squamous cell carcinoma (OSCC) is a serious public health problem, due to its high mortality rate and worldwide rising incidence. OSCC susceptibility is mediated by interactions between genetic and environmental factors. Studies suggest that genetic variants encoding enzymes involved in folate metabolism may modulate OSCC risk by altering DNA synthesis/repair and methylation process.
Objective: The goals of this study were to evaluate the association of three genotypic polymorphism (*MTHFR* C677T, *MTHFR* A1298C and *CBS* 844ins68) and oral cancer risk in southeastern Brazilians and evaluate the interactions between polymorphisms and clinical histopathological parameters.
Methods: This case–control study included 101 cases and 102 controls in the state of Espírito Santo, Brazil. *MTHFR* genotyping was done by PCR-RFLP (polymerase chain reaction – restriction fragment length polymorphism) and *CBS* genotyping by PCR (polymerase chain reaction) analysis.

☆ Please cite this article as: Barbosa A, dos Santos M, de Podestá JR, Gouvêa SA, Von Zeidler SV, Louro ID, et al. Polymorphisms in methylenetetrahydrofolate reductase and cystathionine beta-synthase in oral cancer – a case–control study in southeastern Brazilians. Braz J Otorhinolaryngol. 2016;82:558–66.

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http://dx.doi.org/10.1016/j.bjorl.2015.10.012

Results: *MTHFR* C677T polymorphism was associated with lymph node involvement. Genotype CT + TT acted as a protective factor. *MTHFR* A1298C AC + CC genotype was associated with tumor differentiation, and possibly with a better prognosis. In risk analysis, no correlation was observed between genotypes and OSCC.
Conclusion: We concluded that *MTHFR* C677T, *MTHFR* A1298C and *CBS* 844ins68 polymorphisms were not associated with OSCC risk in southeastern Brazilians; however, we suggest a prognosis effect associated with *MTHFR* C677T and A1298C polymorphisms in OSCC.

PALAVRAS-CHAVE
Carcinoma epidermoide oral;
Metilenotetrahidrofolato redutase;
Cistationina beta-sintase;
Polimorfismo genético

Polimorfismos em metilenotetrahidrofolato redutase, cistationina beta-sintase no câncer de boca – um estudo de caso-controle no Sudeste brasileiro

Resumo
Introdução: O carcinoma espinocelular oral (CECO) trata-se de um importante problema de saúde pública, devido à elevada taxa de mortalidade e incidência crescente em todo o mundo. A susceptibilidade ao CECO é mediada por interações entre fatores genéticos e ambientais. Estudos sugerem que as variantes genéticas que codificam as enzimas envolvidas no metabolismo do folato podem modular o risco de CECO, alterando a síntese/reparação do DNA e o processo de metilação.
Objetivo: Os objetivos deste estudo foram avaliar a associação de três polimorfismos genotípicos (*MTHFR* C677T, *MTHFR* A1298C e *CBS* 844ins68) e o risco de câncer bucal em brasileiros da região Sudeste, e avaliar as interações entre polimorfismos e parâmetros clínico-histopatológicos.
Método: Este estudo de caso-controle incluiu 101 casos e 102 controles no estado do Espírito Santo, Brasil. A genotipagem do polimorfismo *MTHFR* foi realizada por PCR-RFLP (Reação de Polimerase em Cadeia – Polimorfismo no Comprimento de Fragmento de Restrição) e a do *CBS* por análise da PCR (Reação de Polimerase em Cadeia).
Resultados: O polimorfismo *MTHFR* C677T foi associado ao envolvimento de gânglios linfáticos. O genótipo CT + TT atuou como um fator protetor. O genótipo *MTHFR* A1298C AC + CC foi associado à diferenciação do tumor e, possivelmente, a um prognóstico melhor. Na análise de risco, a correlação entre os genótipos e o CECO não foi observada.
Conclusão: Concluímos que os polimorfismos *MTHFR* C677T, *MTHFR* A1298C e *CBS* 844ins68 não estão associados ao risco de CECO nos brasileiros da região Sudeste; no entanto, sugerimos um efeito prognóstico associado aos polimorfismos *MTHFR* C677T e A1298C em CECO.

Introduction

Oral squamous cell carcinoma (OSCC) is the eighth most common human cancer worldwide.[1] In Brazil, nearly 15,290 new cases of oral cancer are expected in 2014, and in the Southeast it is the fourth among men and tenth among women.[2] OSCC is a multifactorial disease, affected by notorious environmental factors such as alcohol and tobacco, as well as genetic factors, of which little is known. Polymorphisms in certain genes may confer susceptibility to OSCC development. Studies have shown a relationship between polymorphisms of genes involved in folate metabolism and OSCC risk due to their influence on methylation, synthesis and DNA repair.[3–7]

MTHFR gene encodes the methylenetetrahydrofolate reductase enzyme, that is important for intracellular folate homeostasis and the irreversible conversion of 5,10-methylenetetrahydrofolate (5,10-MTHF) into 5-methyltetrahydrofolate (5-MTHF). Polymorphisms C677T and A1298C in the *MTHFR* gene may be associated with oral cancer susceptibility due to changes in catalytic activity. The C677T polymorphism results in an enzyme with 65 percent of the wild-type homozygote activity for heterozygotes and 30 percent for homozygotes of the variant allele.[8,9] The *MTHFR* A1298C polymorphism is localized in the regulatory domain region.[10] Homozygous 1298C individuals have approximately the same enzyme activity of those who are heterozygous.[11] Reduced MTHFR enzyme activity increases the availability