INPLASY PROTOCOL

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Support: **None.**

Review Stage at time of this submission: **Piloting of the study selection process.**

Conflicts of interest:
None.

Polymorphisms of Folate-Metabolizing Enzymes (MTHFR, MTR and MTRR) and Colorectal Cancer Risk: An Updated Systematic Review and Meta-analysis of Case-control Studies

El Bairi, K[1]; Azzam, F[2].

Review question / Objective: **Is there an association between gene polymorphisms in MTHFR, MTR and MTRR genes and colorectal cancer risk ?**
Rationale: **Several lines of evidence based on case-control studies suggest that MTHFR, MTR, and MTRR polymorphisms may increase the risk of colorectal cancer in the general population. To increase power and precision as well as to appraise the polished literature, we conducted this updated PRISMA-compliant systematic review and meta-analysis.**
Condition being studied: **Colorectal cancer.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 10 June 2020 and was last updated on 10 June 2020 (registration number INPLASY202060037).

INTRODUCTION

Review question / Objective: **Is there an association between gene polymorphisms in MTHFR, MTR and MTRR genes and colorectal cancer risk ?**

Rationale: **Several lines of evidence based on case-control studies suggest that MTHFR, MTR, and MTRR polymorphisms may increase the risk of colorectal cancer in the general population. To increase power and precision as well as to appraise the polished literature, we conducted this**

updated PRISMA-compliant systematic review and meta-analysis.

Condition being studied: Colorectal cancer.

METHODS

Search strategy: 1-Pubmed/Medline MeSH database: (US National Library of Medicine®): ((((("Colorectal Neoplasms"[Mesh]) AND "Polymorphism, Genetic"[Mesh]) AND "Methylenetetrahydrofolate Reductase (NADPH2)"[Mesh]) OR "5-Methyltetrahydrofolate-Homocysteine S-Methyltransferase"[Mesh]) OR "methionine synthase reductase" [Supplementary Concept]. 2-Keywords on Scopus (Elsevier®), and Web of Science (Clarivate Analytics®): "colorectal cancer" "polymorphism", "MTHFR", "MTR", and "MTRR". 3-Cross-referencing by looking at the references of previously published original articles and systematic reviews.

Participant or population: Included association studies met three criteria: they must (a) evaluated associations between MTHFR, MTR and MTRR polymorphisms and the susceptibility to develop CRC in diverse populations, (b) used a case-control design, and (c) included genotypic frequencies.

Intervention: Polymorphisms of one-carbon metabolizing enzymes including MTHFR (C677T, rs1801133), MTHFR (A1298C, rs1801131), MTR (A2756G, rs1805087) and MTRR (A66G, rs1801394) in colorectal cancer patients.

Comparator: Controls with no history of diseases.

Study designs to be included: Case-control studies.

Eligibility criteria: Included association studies met three criteria: they must (a) evaluated associations between MTHFR, MTR and MTRR polymorphisms and the susceptibility to develop CRC in diverse populations, (b) used a case-control design, and (c) included genotypic frequencies.

Information sources: Pubmed/Medline, Scopus, and Web of Science; Cross-referencing.

Main outcome(s): Risk of colorectal cancer.

Data management: Data extraction and analysis will be conducted by two independent reviewers (Khalid El Bairi and Falak Azzam).

Quality assessment / Risk of bias analysis: Newcastle-Ottawa scale will be used to appraise the included studies.

Strategy of data synthesis: PRISMA guidelines will be used and applied. Appraisal of selected studies using the Newcastle-Ottawa scale. A meta-analysis of ORs (pooling OR) with heterogeneity verification, publication bias, etc.

Subgroup analysis: Different polymorphisms and haplotypes will be assessed using case-control studies with eligibility criteria.

Sensibility analysis: Will not be conducted.

Language: English.

Country(ies) involved: Morocco.

Keywords: Colorectal Cancer, MTHFR, MTR, MTRR, polymorphisms, SNPs, case-control, meta-analysis, Morocco.

Dissemination plans: Publication in an international peer-reviewed and Medline-indexed journal.

Contributions of each author:
Author 1 - Khalid El Bairi - Literature search and data extraction Data analysis and manuscript writing.
Author 2 - Falak Azzam - Literature search and data extraction; Data analysis and manuscript writing.