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Genetic Biomarkers as Potential Non-Invasive Diagnostic Tool for the Detection of Colorectal Cancer

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Introduction

Although the rate of people diagnosed with colorectal cancer has decreased overall since the 1980s, the rate of people younger than 55 years has increased consistently since the 1990s. In addition, colorectal cancer is the second most common cause of death in the United States for men and women combined and death rates have been increasing by at least 1% every year in people younger than 55 years of age.

Globally, the rising incidence of colorectal cancer has now seen itself placed as the third leading cause of cancer-related death among young adults under age 50.

Limitations

Most of the cancer biomarkers having undergone research are proteins which reserve the limitation of not being cancer-specific. Genetic biomarkers possess greater reliability, but genetic changes have not been identified for every cancer type.

Other limitations include sample collection, transportation, representative tissue being processed, reference standards, sensitivity and specificity of assay method, and post-analyses.

The greatest limitation is the translation of biomarkers from a laboratory identification and isolation setting to clinical interpretation and usage.

Background

ctDNA

- Colorectal cancer's tumor components shed significantly, enabling effective liquid biopsy
- Circulating tumor DNA (ctDNA) mirrors tumor genomics for mutation analysis
- ctDNA aids in detecting residual disease, monitoring recurrence, profiling, and predicting therapy response

Epigenetic Changes

- Reversible changes to the genome's phenotypic expression
- Hypo- and hyper-methylation of DNA can lead to CRC by activating transposable elements, removing imprinting, and disrupting the stability of chromosomes

mRNA

- Knockout models both *in vitro* and *in vivo* have shown that reduced expression of SNHG1 reduced the presence of colorectal cancer cells
- Studies have elucidated SNHG1 may confer an oncogenic effect on colorectal cancer and suggest a potential target for its diagnosis and treatment

RNA

- Exosomal noncoding RNA regions are potential biomarkers for liquid biopsy
- Freely circulating miRNA silences genes post-transcriptionally, and its content has been found to be significantly higher in CRC exosomes
- lcnRNAs interact with chromatin-modifying proteins and transcription factors and are associated with tumorigenesis and metastasis in several cancers
- circRNA interacts with RNA-binding proteins to regulate transcription and alternative splicing and are potential targets due to their implication in initiation and progression

Exosomes

- Extracellular vesicles of diverse biomolecules (DNA, RNA, microRNA)
- Role regulating immune response, promoting tumor growth and metastasis, and developing resistance to chemotherapeutic drugs

Metabolites

- SCFAs from dietary fiber enhance intestinal health via GPCR activation and HDAC inhibition
- CRC patients have reduced SCFAs and SCFA-producing bacteria
- SCFA-producing probiotics can inhibit tumors and enhance chemo/immunotherapy in CRC

Microbiota

- Several bacteria have been associated with CRC such as Strep. bovis, Fusobacterium nucleatum, E. coli among others
- Changes to gut microbiota promotes chemokine production and activation of T immune cells leading to inflammation

Methods

The data was collected from a compilation of systematic reviews published on PubMed.
To refine the results, an advanced search featuring ”Liquid Biopsy in Colon Cancer" with systematic review selected as the sole article type and a publication date limit of the past ten years yielded a total of 204 systematic reviews. Henceforth, search terms such as ”non-invasive," ”screening," and "detection" were employed, reducing the number of results to 15. These were analyzed to evaluate various genetic biomarkers as diagnostic tools for colorectal cancer.

Going Forward

The potential for the development of new non-invasive screening methods for the detection of colorectal cancer and the advent of new investigations illuminating the numerous processes and mechanisms implicated in the genesis of colorectal cancer is wide and varied. Although, there have been several mechanisms established, the necessity remains to solidify a viable solution to the problem. It is the aim of this meta-analytical literature review to circumscribe the potentially viable mechanisms whereby screening methods for the early, non-invasive detection of colorectal cancer might be accomplished. These include liquid biopsy, RNA, ctDNA, and mRNA markers,
exosomes, metabolites, and microbiota.

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References

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