The influence of maternal factors on the risk of developing colorectal cancer: A systematic review

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ABSTRACT

Introduction: Colorectal cancer (CRC) is a leading cause of global morbidity and mortality, ranking among the three most commonly diagnosed cancers worldwide. While lifestyle and genetic determinants are well established, the contribution of maternal and reproductive factors remains less clearly defined. Increasing incidence among women has prompted interest in sex-specific mechanisms, particularly the role of oestrogen in colorectal carcinogenesis. Oestrogen is hypothesised to exert a protective effect through oestrogen receptor-beta, expressed in colonic epithelium, where it may reduce cellular proliferation and promote tumour suppression. This systematic review synthesises contemporary epidemiological evidence to evaluate associations between maternal and reproductive exposures and CRC risk. **Materials and Methods:** A systematic review was conducted in accordance with PRISMA guidelines. Electronic databases, including PubMed, Scopus, and Web of Science, were searched for studies published between 2014 and 2025. Eligible studies included prospective cohort, retrospective cohort, and case-control designs examining reproductive or maternal risk factors for CRC. Data were extracted and synthesised narratively from 25 studies. Extracted variables included study design, effect measures (hazard ratios, odds ratios, relative risks, incidence rate ratios, and standardised incidence ratios), corresponding 95% confidence intervals, and adjustment for confounders. Maternal exposures assessed included parity, age at menarche, pregnancy complications, birth outcomes, miscarriage, breastfeeding, hysterectomy, multiple gestation, menstrual irregularity, and use of hormonal therapies such as oral contraceptives and hormone replacement therapy. Studies represented diverse populations across Europe, North America, East Asia, and Nordic regions, enhancing generalisability. Associations were interpreted based on magnitude, direction, and statistical precision. **Results:** Findings across studies were heterogeneous. Protective associations were observed for parity (OR 0.67; HR 0.80), breastfeeding for at least one year (OR 0.74), and hormone replacement therapy (HR 0.57; RR 0.94). In contrast, increased risks were associated with hysterectomy (HR 1.406), multiple gestation (IRR 1.22), irregular menstrual cycles during adolescence (HR 1.36), and large-for-gestational-age births (HR 1.08). Associations with age at menarche were inconsistent, with some studies demonstrating a slight reduction in risk per increasing year (HR 0.97), while others reported no significant relationship. This variability may reflect differences in population characteristics, exposure definitions, and adjustment for confounders such as body mass index and hormonal use. Several exposures, including placental abruption, spontaneous miscarriage, age at first delivery ≥40 years, and serial endometrial thickness, showed no statistically significant association with CRC risk. Confounder adjustment varied substantially across studies, with inconsistent inclusion of lifestyle and metabolic variables. Notably, few studies stratified outcomes by tumour location or molecular subtype, potentially obscuring site-specific or biologically distinct associations. Maternal and reproductive factors demonstrate modest but clinically relevant associations with CRC risk. Parity, breastfeeding, and hormone therapy appear protective, whereas hysterectomy, multiple gestation, and menstrual irregularity may increase risk. **Conclusion:** These findings support hypothesis that cumulative hormonal exposure influences colorectal carcinogenesis through endocrine and metabolic pathways. However, heterogeneity in study design, exposure definitions, and confounder adjustment limits interpretability. Future research should prioritise large, standardised prospective studies with robust adjustment for confounders and stratification by tumour site, menopausal status, and ethnicity. A clearer understanding of these relationships may improve risk stratification and inform prevention strategies in women.