ORIGINAL ARTICLE

Age- and Sex-Stratified Transcriptomic Profiling of Colon Adenocarcinoma Reveals Autosomal and Functionally Relevant Sex-Chromosome Signatures

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ABSTRACT

Background: Colon adenocarcinoma exhibits significant biological heterogeneity, and age- and sex-specific differences may shape its transcriptomic landscape. However, the roles of autosomal and sex-associated molecular signatures in early- and late-onset disease remain poorly defined.

Objective: To identify age- and sex-stratified transcriptomic signatures in colon adenocarcinoma and evaluate their biological relevance in metabolic, inflammatory, and growth signaling pathways.

Methods: This research was performed as a secondary analysis. Transcriptomic and clinical data were obtained from The Cancer Genome Atlas (TCGA) colon adenocarcinoma cohort (n = 460) and the NCBI Gene Expression Omnibus dataset GSE213092. Patients were stratified into early-onset (<50 years) and late-onset (≥ 50 years) groups, with further sex-based analysis. Differential gene expression analysis was performed using DESeq2 for TCGA data and GEO2R/limma for the GEO cohort. Variance-stabilizing transformation, principal component analysis, volcano plots, heatmaps, and protein–protein interaction network analysis were used to interpret the data.

Results: In early-onset disease, female tumors showed enrichment of IGF2 and MAGEA family genes, indicating altered growth signaling and immune evasion, while male tumors demonstrated KDM5D-associated epigenetic regulation, a Y-linked gene with an established tumor-intrinsic role distinct from baseline sex-chromosome dosage effects. In the Korean cohort, CPS1 and CXCL5 were prominently upregulated in early-onset cases, reflecting metabolic and inflammatory alterations. In late-onset disease, female tumors showed enrichment of CALB1 and immune-related transcripts such as CST7, whereas male tumors again showed strong KDM5D expression. Protein–protein interaction analysis revealed highly interconnected gene clusters driven primarily by gene family homology.

Conclusion: Colon adenocarcinoma demonstrates distinct age- and sex-associated transcriptomic heterogeneity driven by autosomal pathways involving metabolism, immune regulation, calcium signaling, and epigenetic control.

Keywords: *Colon adenocarcinoma (COAD), early-onset colorectal cancer (EO-CRC), differential gene expression, Sex-stratified transcriptomics, tumor microenvironment.*

INTRODUCTION

In recent years, there has been a significant change in the clinical presentation of colorectal cancer, with an increase in the frequency of early-onset CRC among patients under 50 years [1]. This epidemiological shift has led to the recognition of EO-CRC as a distinct clinico-molecular subtype of CRC. It is characterized by more aggressive biology and a transcriptomic profile distinct from that of LO-CRC [2]. Despite extensive genomic characterization of CRC, classical models of colorectal carcinogenesis remain overly generalized, focusing on canonical mutations while largely overlooking molecular divergence associated with patient age and sex [3, 4]. Although sex-based differences in clinical outcomes have been observed, the mechanisms driving age- and sex-stratified expression programs, particularly those related to metabolism, inflammation, and growth signaling, remain poorly understood. To address this gap, our study uses a four-quadrant analytical matrix that stratifies patients by age (early-onset *versus* late-onset) and sex (male *versus* female).

Distinct transcriptional changes characterize EO-CRC, especially those associated with metabolic programming and inflammation in autosomal networks. There are significant metabolic changes in the pathogenesis of tumor development in young patients, as evidenced by

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studies conducted specifically in certain populations, including the Korean population [5]. In this regard, carbamoyl-phosphate synthase 1 (CPS1) is one of the metabolically regulated enzymes that exhibit marked differential expression, thus relating nitrogen metabolism to cancer development [5]. The metabolic shift also coincides with alterations in the inflammatory environment, characterized by increased expression of cytokines such as CXCL5, thereby facilitating immune cell infiltration into tumors [6]. On the other hand, activation of developmental pathways through the expression of the homeobox gene VENTX indicates an increased proliferative capacity of EO-CRC cells [7].

Secondly, within these age groups, sex stratification shows other ways in which these tumors can be differentiated. In the early-onset quadrant, there is an enrichment of growth factor signaling in the colonic microenvironment of young female patients. The upregulation of insulin-like growth factor 2 (IGF2) indicates activation of the IGF-1R/PI3K/Akt signaling pathways, which are known to occur due to loss of genomic imprinting and colorectal tumorigenesis [8]. Moreover, the activation of cancer testis antigens, such as MAGEA3, suggests immune evasion in the tumor microenvironment [9]. Female-biased expression of developmental regulators, including SOX1, may further enhance stemness and cellular plasticity in these tumors. On the other hand, the transcriptome of LO-CRC possesses epithelial integrity and mucosal homeostasis-related signatures. Older patients show enrichment of transcriptional programs relevant to epithelial protection, driven by increased expression of calbindin 1 (CALB1), a critical factor involved in calcium homeostasis and vitamin D signaling [10]. Downregulation of CALB1 in men, compared with women, could indicate differential susceptibility to calcium-dependent tumor-suppression mechanisms between the sexes. Similarly, a differential transcriptional profile of immunity-related genes, such as cystatin F (CST7), indicates marked variation in stromal and immune regulatory functions between EO-CRC and LO-CRC groups [11].

Importantly, a sex difference in gene expression that is due to the sex chromosomes (*e.g.*, ZFY, USP9Y, DDX3Y in males, compared to XIST, TSIX in females) will be automatically included within the stratified transcriptomics for males and females. The genes selected for this study were chosen because they do not show sex-chromosome dosage differences in physiology, only differences due to correct sex classification, and were used as internal markers for the correct sex. Some of these genes on the sex chromosomes, however, including KDM5D, have been reported to have an independent, tumor-intrinsic function that is in addition to dosage effects of the sex chromosomes. Thus, one of the primary objectives of this study was to distinguish pathways involved in cancer from background sex-chromosome dosage effects and to determine whether there are sex-linked genes that have a functional role in cancer.

In the current work, the molecular profile is supplemented by differential gene expression analysis from The Cancer Genome Atlas (TCGA) and NCBI's Gene Expression Omnibus (GEO), including a cohort of Korean patients (GSE213092). By applying DESeq2 analysis and examining protein-protein interactions using the STRING database, the study aims to reveal biological networks associated with age- and sex-specific biomarkers, with an emphasis on autosomal pathways.

MATERIALS AND METHODS

This research was performed as a secondary analysis, an in silico, transcriptome-based study that explored gene expression profiles in colon adenocarcinoma associated with age and sex using public datasets. The entire structure of the research process, including population stratification, data processing methods, and the molecular insights gained, is presented in the Graphical Abstract.

The transcriptomics data and corresponding clinical parameters were retrieved from two publicly accessible databases. The TCGA COAD (The Cancer Genome Atlas, colon adenocarcinoma cohort, https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE213092) database was downloaded from the cBioPortal website (https://www.cbioportal.org/) [12], while the GSE213092 database was processed in GEO2R [13].

TCGA data initially included 463 samples, but three patients were excluded due to the unavailability of mRNA gene expression data, resulting in a final dataset of 460 patients for analysis. On the other hand, the GEO dataset contained patients with primary colon adenocarcinoma collected from Korea. Both datasets were required to include patients with primary colon adenocarcinoma along with mRNA gene expression data and clinical information such as age and sex. Excluded from the subsequent analysis were patients lacking mRNA expression data, duplicates after pre-processing, and transcripts with extremely low gene expression in the dataset. Patients were then classified by age into early-onset (less than 50 years) and late-onset (50 years and older). The 50-year threshold was adopted because it represents the standard clinical definition of early-onset colorectal cancer used in epidemiological and screening guidelines, allowing direct comparability with prior studies on this topic.

The analysis of differential gene expression from TCGA data was done with the aid of DESeq2 software within the R programming suite (version 4.x), whereas that of the GEO datasets was done with the GEO2R tool on a limma-based analysis framework [14]. The threshold criteria for statistically significant gene differential expression include an adjusted p-value < 0.05 using the Benjamini-Hochberg correction, with a minimum |log2 fold change| > 1.0 for TCGA and a strict threshold of> 1.5 for GEO. The normalization of raw count data was performed using a variance-stabilizing transformation (VST), and principal component analysis (PCA) was applied to assess their distribution and variability. Volcano plot, MA plot, and heatmap were used to illustrate the differential gene expression patterns across various groups. Pre-processed mRNA expression data were downloaded directly from cBioPortal for the TCGA cohort, since this had already been performed as part of the standard TCGA/GDC pipeline.

To study protein-protein interactions, the STRING database was used to construct protein networks with a minimum interaction score of 0.400 (*i.e.*, medium confidence) and to subsequently identify clusters, if any, within the PPI network. Functional analysis (Benjamini-Hochberg FDR correction) was performed to identify the biological pathways and processes associated with each DEG cluster.

All analyses were conducted using R (version 4.x). The differential expression analysis was conducted using DESeq2, and multiple hypothesis testing was corrected using the Benjamini-Hochberg FDR approach [15]. Any result that had a p-value < 0.05 after correcting for multiple hypothesis testing was considered to be statistically significant. The current work used publicly available data from the TCGA and GEO databases, so no IRB/ERC approval was required, and all methods were in line with the guidelines of the respective data repositories. While some of the data used were collected more than five years ago, their use is reasonable due to their high quality and relevance.

RESULTS

Sex-Associated Transcriptomic Landscape in Young-Onset Colon Adenocarcinoma

Gene expression analysis in patients under the age of 50 years for differential gene expression by DESeq2 (padj < 0.05, |log2FC| > 1.0) yielded distinct transcriptomes that were sexually specific (**Figs. 1 & 2**). It was unsurprising that the largest statistical differences between samples occurred in X- and Y-chromosome genes and reflected physiology rather than cancer biology. Interesting biological insights included autosomal genes regulating growth factor signaling, immune evasion, and epigenetics (**Tables S1 & S2**).

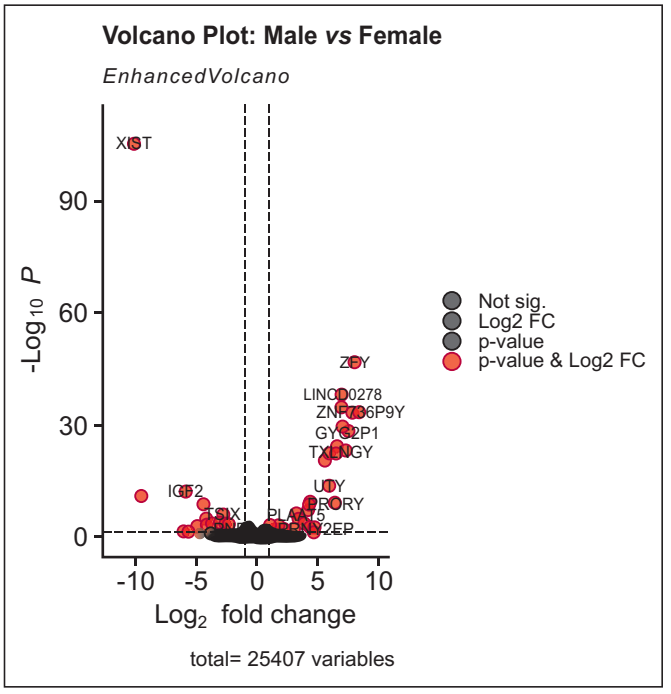

Fig. (1): Volcano plot illustrating the differentially expressed genes between male and female patients in the young-onset colon adenocarcinoma cohort.

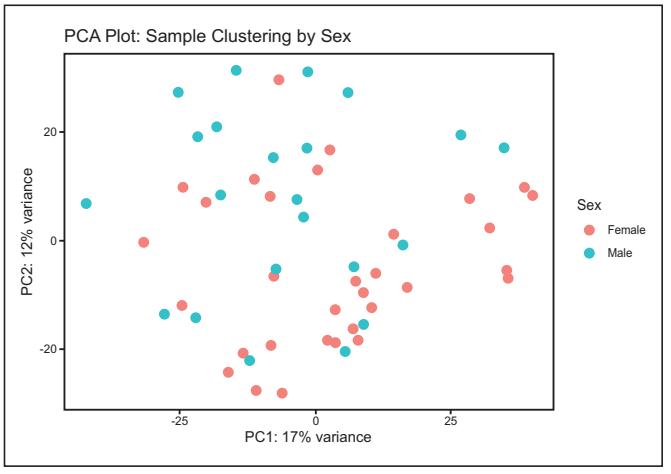

Fig. (2): Principal Component Analysis (PCA) plot demonstrating the clustering of young-onset colon adenocarcinoma samples based on patient sex.

In young-onset female tumors, IGF2 (log2FC = -5.89) was significantly Upregulated compared to males, indicating greater IGF2 enrichment in females and highlighting dependence on the IGF-1R/PI3K/Akt pathway. The observed upregulation of MAGEA3, MAGEA6, and MAGEA12 (log2FC range -9.54 to -4.61) indicates cancer testis antigen-based tumor immunity through down-regulation of p53. SOX1 (log2FC = -4.23) enrichment highlights stemness and epithelial-to-mesenchymal plasticity in young female tumors. For young male tumors, enrichment for MUC5AC (log2FC = 4.26) is associated with mucinous tumors, and enrichment for the Y-linked histone H3K4 demethylase KDM5D (log2FC = 6.64) suggests epigenetic remodeling of the autosomal gene program.

Protein–Protein Interaction Network Analysis: Young-Onset Cohort

The PPI analysis of the top 60 DEGs in the young-onset group (STRING database; minimum interaction score 0.400) showed two major clusters, including proteins from the Y chromosome (ZFY, DDX3Y, USP9Y, KDM5D, EIF1AY, RPS4Y1) and MAGE family members (MAGEA3, MAGEA6, MAGEA12), representing their common chromosomal localization and protein homology (**Fig. 3**). In addition, functional enrichment analysis performed.

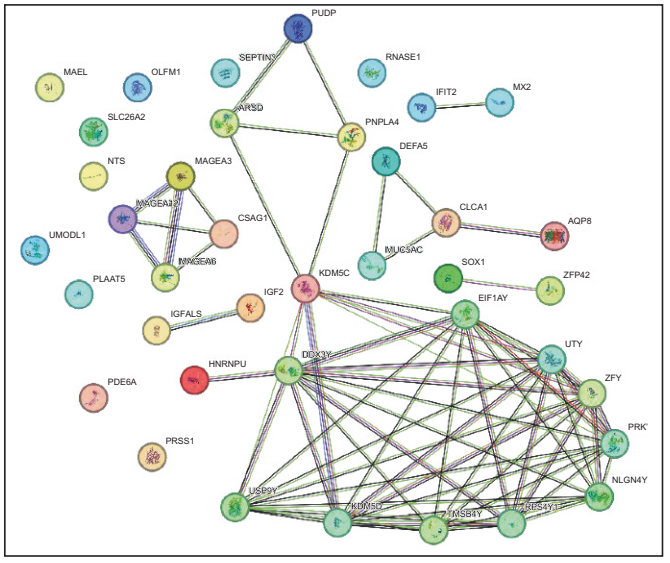

Fig. (3): Protein-protein interaction (PPI) network illustrating functional hubs of Y-linked regulatory elements and MAGE family proteins driving sex-specific colon cancer pathogenesis.

Sex-Associated Transcriptomic Landscape in Late-Onset Colon Adenocarcinoma

Regarding the late-onset group (≥ 50 years), similar differential expression analysis also revealed sex-based gene signatures (**Fig. 4**). Besides the canonical chromosome-level sex genes such as XIST and TSIX or Y-chromosome-encoded genes, some biologically relevant autosome-level genes included CALB1 (log2FC = -2.71, padj = 0.000145), expressed exclusively in female colorectal adenocarcinomas and involved in vitamin D-dependent calcium metabolism in association with established chemoprotective functions in colorectal carcinogenesis. Another female-biased gene, CST7 (log2FC = -2.03, padj = 7.58E-06), encodes a cystatin F protein present in cytotoxic immune cells, suggesting sex-specific tumor immunosurveillance mechanisms. Other genes involved in the immune response included HLA-DRB6 and HLA-DOA, as well as X-linked genes that evade inactivation (KDM5C, KDM6A, ZFX, and PRKX), which were found to be active only in female tumors (**Table S3**).

In male colorectal tumors, both KDM5D (log2FC = 7.94) and UTY (log2FC = 8.26) genes retained their status as the primary epigenetic factors associated with late-onset tumors, consistent with the results in the young-onset cohort. The gene encoding TBL1Y (log2FC = 5.16), a member of the Wnt/ß-catenin corepressor complex, was also observed in male samples and may influence the expression of genes encoding proteins such as MYC and CCND1. Complete statistical parameters for late-onset DEGs are provided in Supplementary Tables **S3** and **S4**.

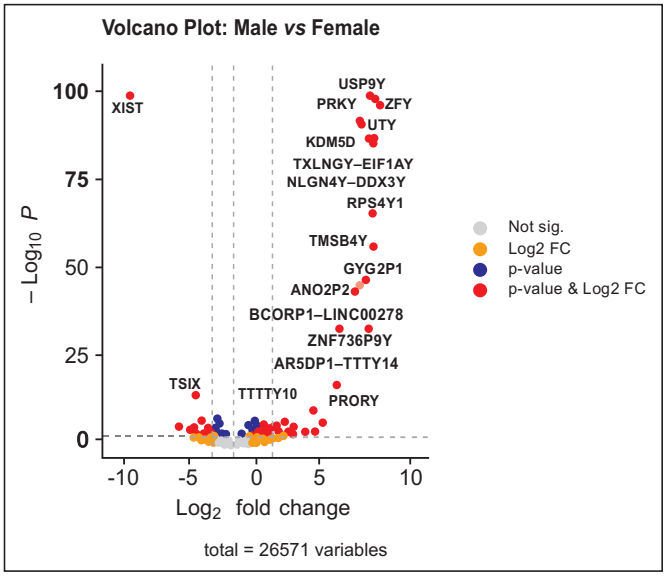

Fig. (4): Volcano plot representing the statistically significantly differentially expressed genes between male and female patients in the late-onset (≥50 years) colon adenocarcinoma group.

Korean Population Cohort: Differential Gene Expression

Using transcriptomic data of the Korean GEO cohort (GSE213092; n ≈70), applying the stringent threshold of |log2FC| > 1.5, we found that the early-onset cases possessed specific molecular signatures (**Fig. 5**). CPS1 turned out to be the gene with the highest degree of upregulation among the cases with early onset (log2FC = 4.144, score = 7.022). It relates to the role of alterations in

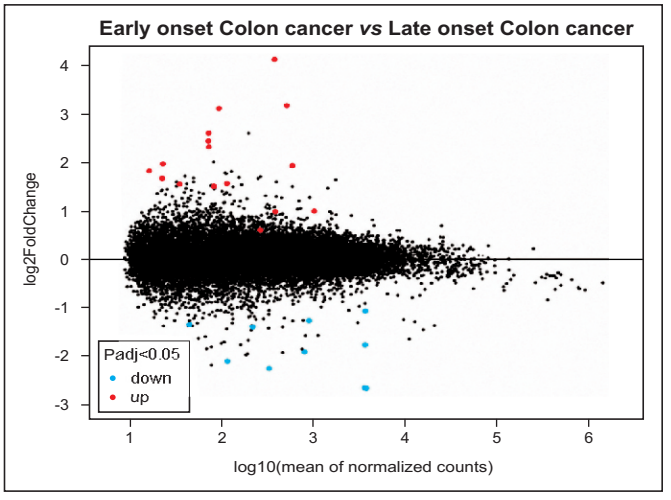

Fig. (5): MA plot comparing the gene expression profiles between early-onset and late-onset colon cancer patients in the Korean dataset to visualize fold change against normalized counts.

nitrogen metabolism in early-onset pathogenesis, consistent with the CMS3 colorectal cancer subtype. Additionally, two genes, CXCL5 (log2FC = 3.125) and VENTX (log2FC = 3.063), were upregulated, showing inflammation-mediated changes in the microenvironment and increased proliferation, respectively (**Table 1**). (Table **S5** shows the biologically important genes upregulated and downregulated in Korean populations).

Table 1: Top upregulated genes in early-onset *vs.* late-onset colon cancer (Korean cohort).

Rank	Gene Symbol	Log_2FC	Score	Functional Relevance
1	CPS1	4.144	7.022	Nitrogen metabolism; CMS3 metabolic subtype marker
2	CXCL5	3.125	3.752	Inflammatory chemokine; immune cell recruitment
3	VENTX	3.063	5.232	Homeobox factor; cancer cell proliferation

On the contrary, IGF2 (log2FC = - 2.742) showed an obvious tendency for downregulation in early-onset samples in concordance with results obtained for the TCGA cohort. In addition, TCN1 and JSRP1 were found to be downregulated as well (**Table 2**).

Table 2: Top downregulated genes in early-onset *vs.* late-onset colon cancer (Korean cohort).

Rank	Gene Symbol	Log_2FC	Score	Functional Relevance
1	IGF2	-2.742	1.504	IGF-1R/PI3K/Akt pathway; growth factor signaling
2	TCN1	-2.327	1.398	Vitamin B12–binding; gastro intestinal cancer biomarker
3	JSRP1	-2.173	3.123	Cellular signaling: possible role in tumor progression

DISCUSSION

Stratifying colon adenocarcinoma by age and sex reveals heterogeneity not detected by conventional analyses [16]. Surely, our analysis identified some sexual signals, such as XIST and some Y-linked genes [17], but these are mostly physiological sex differences and were used primarily as internal validation signals. The more biologically informative findings are those from genes previously known to be associated with colorectal cancer biology, both autosomal and functionally sex-linked. In female patients with young-onset disease, IGF2 was enriched, which is in agreement with the role it has in colorectal cancer. IGF2 is an imprinted growth factor gene which can stimulate the well-characterized colorectal cancer-promoting IGF-1R/PI3K/Akt pathway [18]. When IGF2 is not imprinted, both alleles are expressed, and this has been associated with increased cell proliferation and decreased apoptosis in colorectal tumors [19]. Loss of IGF2 imprinting has also been shown to correlate with early disease onset, advanced disease, right-sided tumor, and low differentiation or mucinous tissue type in previous studies [20]. Our data also support this idea, but actual information on imprinting status would be required to define the mechanism.

Female patients also showed coordinated upregulation of MAGEA3, MAGEA6, and MAGEA12, which are not normally expressed in adult tissues but are reactivated in various cancers, including CRC [21]. These proteins bind TRIM28 and inhibit the expression of p53 target genes, which helps to regulate apoptosis and senescence [22]. Although being involved in immune escape, MAGE upregulation has been linked to poor prognosis and resistance to immune checkpoint blockade, and previous studies demonstrated that MAGEA3 can induce a measurable T-cell response. This sex-biased expression may be linked to a sex-specific pathway to immune escape in young-onset colon cancer, but further functional studies are needed to confirm this. CPS1 was the most significantly upregulated gene in the Korean early-onset group, suggesting that metabolic reprogramming may contribute to early disease onset. Recently, CPS1 was identified as a marker of the CMS3 metabolic subtype [23], characterized by enterocyte-like differentiation and altered metabolism. In this subtype, it is involved in de novo pyrimidine synthesis, and its inhibition decreases proliferation and stemness and induces differentiation, which is not seen in CMS2 or CMS4 tumors [24]. The CPS1 enrichment in this cohort supports the idea that the pathway could be a novel subtype-specific target for early-onset CRC. CALB1 was found to be upregulated in LO patients, particularly females, possibly due to its involvement in calcium uptake by the colon epithelium in response to vitamin D [25]. Estrogen has been suggested to crosstalk with calcium/vitamin D signaling pathways and with Wnt/ß-catenin signaling, as well as with proliferation, differentiation, and apoptosis, all of which are modulated by vitamin D receptor activation [26]. A downward trend in CALB1 in females is also consistent with the lower incidence of colorectal cancer in women, but is not yet understood.

A gene on the Y chromosome, KDM5D, was consistently upregulated in male tumors in both the early- and late-onset groups. In addition to its role as a sex marker, KDM5D has been shown to enhance metastasis and immune resistance in KRAS-mutated CRC by repressing AMOT, a gene associated with cell adhesion [27], and TAP1 and TAP2, which are essential for MHC class I antigen presentation [28]. Our findings are consistent with a potential functional role of KDM5D in male colorectal cancer, but the current study cannot establish causality or confirm the therapeutic relevance of KDM5D. These sex differences are consistent with those seen from an epidemiological perspective. In most areas,

males have a higher incidence and mortality rate of colorectal cancer than females [29]. Premenopausal women (18 to 44 years) have demonstrated improved survival compared to age-matched men and women, a pattern frequently believed to be driven by estrogen signaling, which has been implicated in Wnt/ß-catenin signaling through KCNQ1 channel activation and the membrane estrogen receptor GPER [30]. Genome-wide data also indicate that mutations in BRAF are more prevalent in women, whereas TP53 mutations are more prevalent in men [31], and that additional co-alterations are prevalent: KRAS is common with ATM and ARID1A in early-onset disease, and, in late-onset disease, is mutually exclusive with these mutations.

Our findings are mapped to known molecular subtypes, which supports their biological plausibility. CPS1 is associated with the CMS3 subtype of tumors metabolically defined; IGF2 dysregulation is associated with multiple subtypes, with a stronger association with the right-sided, microsatellite-instable (MSI) subtype; MAGE expression is associated with multiple subtypes and may provide additional immunological stratification; CALB1 expression is associated with more differentiated epithelial tumors; and KDM5D expression in men is associated with KRAS mutation status and metastatic outcome. Collectively, these connections indicate that sex-based stratification of classification schemes may provide valuable insights into colorectal cancer heterogeneity. The genes IGF2, CPS1, and CALB1 are involved in distinct biological processes previously associated with age- or sex-specific colorectal cancer patterns, growth factor signaling, metabolic reprogramming, and calcium regulation, respectively. MAGE family genes (MAGEA3, MAGEA6, MAGEA12) are involved in immune evasion by suppressing p53, and KDM5D is associated with metastasis and immune resistance by silencing genes related to cell adhesion and antigen presentation. Together, these genes constitute complementary mechanisms underlying the sex- and age-based molecular differences observed in this study, including growth, metabolism, and immune evasion.

There are some restrictions to be noted. This study is mainly in silico, secondary data analytics (TCGA and GEO), and the association of any of the findings reported in this study has not been validated with qPCR, IHC, or functional assays. The Korean cohort lacked exact age-at-death data, so existing annotations were used, which may have resulted in some misclassification. Furthermore, the TCGA cohort is small relative to young-onset cases, and tumor stage, microsatellite status, tissue of origin, and stromal composition were not fully adjusted for. Hence, our findings suggest that sex differences exist in the association with colon adenocarcinoma but should be viewed as hypothesis-generating and not causal.

CONCLUSION

Age- and sex-specific molecular heterogeneity is associated with the development of colon adenocarcinoma. Sex-specific associations have also been reported: elevated IGF2 levels and involvement of the IGF-1R/PI3K/Akt growth factor pathway appear more prominent in younger females, while genes from the MAGE cancer-testis antigen family (MAGEA3, MAGEA6, MAGEA12) point to a sex-specific mechanism of immune evasion through p53 inhibition. In the Korean early-onset sample, CPS1 upregulation may indicate metabolic rewiring specific to the CMS3 colorectal cancer subtype and a possible treatment target. In late-onset females, the pronounced elevation of CALB1 highlights the critical role of calcium and vitamin D signaling pathways in maintaining intact epithelial protection and driving sex specific chemoprevention. In males, KDM5D, the Y-chromosome-encoded histone demethylase, may act as a driver of metastatic spread and immunotolerance in colorectal cancer with KRAS mutations. XIST and genes of the Y chromosome (ZFY, USP9Y, DDX3Y) may be associated with physiological sex differences but not with tumor development.

ETHICS APPROVAL

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA

The data supporting the findings of this study are available within the article and its supplementary materials. No new experimental datasets were generated during this research. Any additional information related to the included studies and Bioinformatics validation can be obtained from the corresponding author upon reasonable request.

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CONFLICT OF INTEREST

The authors declare that there are no commercial or financial relationships that could be construed as a potential conflict of interest regarding the publication of this research.

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Declared none.

AUTHORS' CONTRIBUTION

SAH conceptualized the study, designed the research methodology, performed the bioinformatics and statistical analyses, interpreted the data, and drafted the

manuscript. PDB contributed to data interpretation, critical revision of the manuscript, and provided intellectual input on pharmacological and molecular aspects. NM assisted in data pre-processing and annotation and contributed to the bioinformatics workflow. BA contributed to the literature review, data curation, and manuscript drafting. Hamna Tariq assisted with visualization, figure preparation, interpretation of transcriptomic results, and manuscript drafting. IS supervised the study, contributed to study design refinement, critically revised the manuscript, and finalized the version for publication.

All authors read and approved the final manuscript.

SUPPLEMENTARY MATERIAL

Supplementary material is available on the journal's website.

REFERENCES

1. Ullah F, Pillai AB, Omar N, Dima D, Harichand S. Early-onset colorectal cancer: Current insights. Cancers (Basel) 2023; 15(12): 3202. DOI: https://doi.org/10.3390/cancers15123202

2. Mi X, Zheng P, Wu X. Differential analysis of early-onset and late-onset colorectal cancer based on multidimensional evidence integration: A review. Cancer Control 2025; 32: 10732748251363337. DOI: https://doi.org/10.1177/10732748251363337

3. Barna R, Dema A, Jurescu A, Vaduva AO, Lazureanu DC, Viţa O, *et al.* The relevance of sex and age as non-modifiable risk factors in relation to clinical-pathological parameters in colorectal cancer. Life 2025; 15(2): 156. DOI: https://doi.org/10.3390/life15020156

4. Choi Y, Kim N. Sex difference of colon adenoma pathway and colorectal carcinogenesis. World J Mens Health 2024; 42(2): 256-82. DOI: https://doi.org/10.5534/wjmh.230085

5. Kim JY, Ha YJ, Park S-J, Lee S-W, Kim S-Y, Oh S-E, *et al.* Whole-genome sequencing data of early- and late-onset colorectal cancer in 99 Korean patients. Scientific Data 2026; 13(1): 198. DOI: https://doi.org/10.1038/s41597-025-06517-0

6. Deng J, Jiang R, Meng E, Wu H. CXCL5: A coachman to drive cancer progression. Front Oncol 2022; 12: 944494. DOI: https://doi.org/10.3389/fonc.2022.944494

7. Kumar S, Kumar V, Li W, Kim J. Ventx family and its functional similarities with nanog: involvement in embryonic development and cancer progression. Int J Mol Sci 2022; 23(5): 2741. DOI: https://doi.org/10.3390/ijms23052741

8. Blyth AJ, Kirk NS, Forbes BE. Understanding IGF-II action through insights into receptor binding and activation. Cells 2020; 9(10): 2276. DOI: https://doi.org/10.3390/cells9102276

9. Wang Y, Song X, Zheng Y, Liu Z, Li Y, Qian X, *et al.* Cancer/testis Antigen MAGEA3 interacts with STAT1 and remodels the tumor microenvironment. Int J Med Sci 2018; 15(14): 1702-12. DOI: https://doi.org/10.7150/ijms.27643

10. Cao LQ, Wang YN, Liang M, Pan MZ. CALB1 enhances the interaction between p53 and MDM2 and inhibits senescence in ovarian cancer cells. Mol Med Rep 2019; 19(6): 5097-104. DOI: https://doi.org/10.3892/mmr.2019.10212

11. Xu H, Liu W, Kuang X, Zhao J, Wang X, Li B. Expression profiles and clinical significance of cystatin family genes in transitional cell carcinoma of the urinary bladder. Bladder 2025; 12(1): e21200035. DOI: https://doi.org/10.14440/bladder.2024.0057

12. Gao J, Aksoy BA, Dogrusoz U, Dresdner G, Gross B, Sumer SO, *et al.* Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Sci Signal 2013; 6(269): pl1. DOI: https://doi.org/10.1126/scisignal.2004088

13. Clough E, Barrett T, Wilhite SE, Ledoux P, Evangelista C, Kim IF, *et al.* NCBI GEO: archive for gene expression and epigenomics data sets: 23-year update. Nucleic Acids Res 2024; 52(D1): D138-44. DOI: https://doi.org/10.1093/nar/gkad965

14. Love MI, Huber W, Anders S. Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2. Genome Biol 2014; 15(12): 550. DOI: https://doi.org/10.1186/s13059-014-0550-8

15. Chen X, Robinson DG, Storey JD. The functional false discovery rate with applications to genomics. Biostatistics 2021; 22(1): 68-81. DOI: https://doi.org/10.1093/biostatistics/kxz010

16. Abancens M, Bustos V, Harvey H, McBryan J, Harvey BJ. Sexual dimorphism in colon cancer. Front Oncol 2020; 10: 607909. DOI: https://doi.org/10.3389/fonc.2020.607909

17. Lopes-Ramos CM, Quackenbush J, DeMeo DL. Genome-wide sex and gender differences in cancer. Front Oncol 2020; 10: 597788. DOI: https://doi.org/10.3389/fonc.2020.597788

18. Zhao X, Li X, Ren Q, Tian J, Chen J. Calycosin induces apoptosis in colorectal cancer cells, through modulating the ERß/MiR-95 and IGF-1R, PI3K/Akt signaling pathways. Gene 2016; 591(1): 123-8. DOI: https://doi.org/10.1016/j.gene.2016.07.012

19. Gao T, Liu X, He B, Pan Y, Wang S. IGF2 loss of imprinting enhances colorectal cancer stem cells pluripotency by promoting tumor autophagy. Aging (Albany NY) 2020; 12(21): 21236-52. DOI: https://doi.org/10.18632/aging.103837

20. Yang Q, Qu R, Lu S, Zhang Y, Zhang Z, Fu W. Biological and clinical characteristics of proximal colon cancer: far from its anatomical subsite. Int J Med Sci 2024; 21(10): 1824. DOI: 10.7150/ijms.97574

21. Almutairi MH, Alotaibi MM, Alonaizan R, Alrefaei AF, Almutairi BO. Identification of MAGE-A family genes in colon cancer patients and their expression mechanism. J King Saud Univ Sci 2022; 34(7): 102251. DOI: 10.1016/j.jksus.2022.102251

22. Chiang C, Yap BK. TRIM25, TRIM28 and TRIM59 and their protein partners in cancer signaling crosstalk: Potential novel therapeutic targets for cancer. Curr Issues Mol Biol 2024; 46(10): 10745-61. DOI: https://doi.org/10.3390/cimb46100638

23. Lee YY, Li CF, Lin CY, Lee SW, Sheu MJ, Lin LC, *et al.* Overexpression of CPS1 is an independent negative prognosticator in rectal cancers receiving concurrent chemoradiotherapy. Tumor Biol 2014; 35(11): 11097-105. DOI: https://doi.org/10.1007/s13277-014-2425-8

24. Torang A, Kirov AB, Lammers V, Cameron K, Wouters VM, Jackstadt RF, *et al.* Enterocyte-like differentiation defines metabolic gene signatures of CMS3 colorectal cancers and provides therapeutic vulnerability. Nat Commun 2025; 16(1): 264. DOI: https://doi.org/10.1038/s41467-024-55574-3

25. Devall MA, Dampier CH, Eaton S, Ali MW, Plummer SJ, Bryant J, *et al.* Transcriptomic response to calcium in normal colon organoids is impacted by colon location and sex. Cancer Prev Res 2022; 15(10): 679-88. DOI: https://doi.org/10.1158/1940-6207.capr-22-0068

26. Na SY, Kim KB, Lim YJ, Song HJ. Vitamin D and colorectal cancer: current perspectives and future directions. J Cancer Prev 2022; 27(3): 147-156. DOI: https://doi.org/10.15430/JCP.2022.27.3.147

27. Li J, Lan Z, Liao W, Horner JW, Xu X, Liu J, *et al.* Histone demethylase KDM5D upregulation drives sex differences in colon cancer. Nature 2023; 619(7970): 632-9. DOI: https://doi.org/10.1038/s41586-023-06254-7

28. Mantel I, Sadiq BA, Blander JM. Spotlight on TAP and its vital role in antigen presentation and cross-presentation. Mol Immunol 2022; 142: 105-19. DOI: 10.1016/j.molimm.2021.12.013

29. Wu S, Zhang Y, Lin Z, Wei M. Global burden of colorectal cancer in 2022 and projections to 2050: incidence and mortality estimates from GLOBOCAN. BMC Cancer 2025; 25(1): 1770. DOI: https://doi.org/10.1186/s12885-025-15138-0

30. Harvey BJ, Harvey HM. Sex differences in colon cancer: Genomic and nongenomic signalling of oestrogen. Genes 2023; 14(12): 2225. DOI: https://doi.org/10.3390/genes14122225

31. Tsilimigras DI, Stecko H, Ntanasis-Stathopoulos I, Pawlik TM. Racial and sex differences in genomic profiling of intrahepatic cholangiocarcinoma. Ann Surg Oncol 2024; 31(13): 9071-8. DOI: https://doi.org/10.1245/s10434-024-16141-8