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The Tumor Trail: From Genetic Alterations to Targeted Therapies in Colorectal Cancer

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ABSTRACT: Colorectal cancer (CRC) is the third most diagnosed cancer and the second leading cause of cancer deaths globally. Projections indicate a 60–71.5% increase in CRC mortality by 2035, especially in developing countries adopting Western dietary habits. Although genetic factors account for around 25% of cases, lifestyle-related risk factors such as obesity, inactivity, and unhealthy diets play a major role. CRC generally develops through three pathways: sporadic (70%), hereditary (25%), and colitis-associated (5%), often following a slow 10–15 year adenoma-to-carcinoma progression. Current diagnostic tools, including fecal tests and endoscopy, miss many early-stage cases. Treatment typically involves surgery, chemotherapy (e.g., 5-FU, oxaliplatin, irinotecan), and targeted therapies, with immunotherapy emerging as a promising option. However, issues like late-stage diagnosis, therapy resistance, and recurrence remain prevalent. Research is increasingly focused on enhancing early detection via liquid biopsies and tailoring prevention through screening and lifestyle interventions to better manage CRC worldwide.

KEYWORDS: Colorectal Cancer, Deadliest Cancer, Fecal tests, Colon, Rectum, Lifestyle, Pharmacotherapy, Chemotherapy, Biopsy.

I. INTRODUCTION

Colorectal cancer (CRC), comprising colon and rectal malignancies, is the third most diagnosed cancer and the second leading cause of cancer-related deaths globally, responsible for 9.4% of cancer deaths in 2020 [1,2,3]. Its incidence is rising, particularly in aging populations and developing nations, with cases expected to more than double by 2035 [4]. Though it ranks third in overall incidence (6.1%), CRC is second in mortality (9.2%) due to regional disparities linked to socioeconomic conditions [5,6,7].

Modifiable lifestyle factors such as obesity, physical inactivity, and unhealthy diets significantly contribute to CRC risk, while regular exercise offers protection [8,9]. The shift toward Western dietary habits in developing regions has further elevated CRC incidence [10].Genetic predisposition accounts for nearly 25% of CRC incidence [11]. CRC develops from gland-forming epithelial cells in the large intestine and is categorized as sporadic, hereditary, or inflammation-related [12,13].

Screening programs in developed regions have successfully reduced CRC mortality by detecting precancerous lesions early [14,15]. The slow adenoma-to-carcinoma transition (10–15 years) allows for preventive interventions like polyp removal [16,17,18,19]. High-risk groups benefit from intensified surveillance using stool tests and endoscopy [20,21]. Nonetheless, early detection remains suboptimal, and challenges like recurrence and treatment resistance persist [22].

II. EPIDEMIOLOGY

Mortality

According to GLOBOCAN 2020 data, colorectal cancer (CRC) ranks as the second leading cause of global cancer-related deaths, causing approximately 935,000 deaths and an age-standardized mortality rate (ASMR) of 9.0 per 100,000 annually. Europe recorded the highest mortality (ASMR 12.3), while Africa (5.6) and the Eastern Mediterranean (5.3) had the lowest. Intermediate mortality rates were observed in Oceania (9.3), Asia (8.6), Latin America (8.2), and North America (8.2). Males had higher mortality (ASMR 11.0) than females (7.2), with over

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515,000 and 419,000 deaths, respectively [23,24,25].

Incidence

In 2020, colorectal cancer (CRC) ranked as the third most prevalent cancer worldwide, with 1.93 million new cases and an age-standardized rate (ASR) of 19.5 per 100,000. Incidence was highest in Europe (30.4), Oceania (29.8), and North America (26.2), but lowest in Africa (8.4) and the Eastern Mediterranean (9.1). Hungary recorded the highest national ASR (45.3), while Guinea had the lowest (3.3) (23,24,25). Wealthier regions and those with very high HDI showed significantly higher rates (30.2 and 29.4) than low-income and low-HDI areas (8.8 and 7.4).

Time Trends and Future Burden

While incidence rates have stabilized or declined in countries like the U.S., Canada, and Australia, nations undergoing rapid development, including Brazil, Costa Rica, and India, show rising trends [26,27,28,29,30,31]. Projections indicate that CRC cases will rise from 1.93 million in 2020 to 3.15 million by 2040. The most significant increases are anticipated in Africa (95.0%), the Eastern Mediterranean (92.0%), Latin America (74.0%), and Asia (70.8%), while very high HDI countries are expected to see a smaller rise (35.0%) [32].

Early-Onset CRC

Early-onset colorectal cancer (EOCRC), diagnosed before age 50, is increasing globally, with 188,069 cases and an ASR of 2.9 per 100,000 [33,34,35,36,37,38,39,40]. North America (6.1) and Oceania (5.3) have the highest rates, while Africa (2.0) and Asia (2.6) are lower. EOCRC is rising in both developed and developing countries [41,42,43,44,45]. Contributing factors include genetic predisposition, obesity, poor diet, physical inactivity, alcohol, low vitamin D, inflammatory conditions, and gut microbiome imbalance [46,47]. This trend emphasizes the need for targeted surveillance and age-adapted screening strategies.

III. ETIOLOGY

The majority of colon cancer instances (approximately 70%) develop sporadically, indicating they arise without identifiable hereditary predisposition. However, 3% to 5% of cases are linked to known genetic mutations, such as those seen in hereditary nonpolyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP). A significant proportion (20-25%) of colorectal cancer patients present with a well-documented family history of the disease, yet lack identifiable germline mutations associated with hereditary cancer syndromes.

Risk Factors for Colon Cancer

- **Age:** Sporadic colon cancer predominantly affects older populations, with a median diagnosis age exceeding 65 years.
- **Family History:** Having a close relative with colon cancer increases an individual's risk.
- **Inherited Genetic Syndromes:** Conditions like HNPCC, FAP, and Peutz-Jeghers syndrome significantly elevate the risk of developing colon cancer [48,49].
- **Precancerous Polyps:** Adenomas detected during colonoscopy—particularly villous adenomas and sessile serrated polyps—pose a higher risk of malignancy.
- **Inflammatory Bowel Disease (IBD):**
  - Patients with ulcerative colitis have a 0.5% yearly cancer risk in the initial 10-20 years, which escalates to 1% annually thereafter.
  - Crohn's disease may also increase risk, primarily in the ileocolic region(50).
- **Lifestyle and Environmental Factors:**
  - Alcohol consumption, smoking, obesity, and diets high in processed red meat.
  - Insulin resistance, prior radiation exposure, and immunosuppression [51,52].

Protective Factors Against Colon Cancer

Research suggests several factors may help reduce the risk of colon cancer:

- **Dietary Choices:** High intake of fruits, vegetables, fiber, resistant starch, fish, garlic, and coffee.
- **Supplements:** Folate, folic acid, pyridoxine (vitamin B6), calcium, vitamin D, and magnesium.
- **Medications:**
  - Aspirin and other NSAIDs.
  - Hormone replacement therapy in postmenopausal women.
  - Statins, bisphosphonates, and angiotensin inhibitors.
- **Physical Activity:** Regular physical activity correlates with reduced CRC risk [53].

IV. PATHOPHYSIOLOGY

Colorectal cancer (CRC) develops through progressive genetic alterations, driven by three main molecular pathways: chromosomal instability

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(CIN), mismatch repair deficiency (MMR), and the CpG island methylator phenotype (CIMP) [54]. The CIN pathway, associated with the adenoma-carcinoma sequence, involves APC mutations (~60% of cases), KRAS and TP53 mutations, and occasional BRAF mutations, disrupting Wnt/β-catenin signaling and promoting tumor progression. The MMR-deficient pathway results from mutations in genes like MLH1, MSH2, MSH6, or PMS2, leading to microsatellite instability (MSI) [55]. These tumors, often located in the right colon, are mucinous or poorly differentiated, less responsive to 5-FU, but more amenable to immunotherapy. The CIMP pathway (~15% of CRCs) features hypermethylation of CpG island promoters, frequent KRAS/BRAF mutations, and is commonly associated with serrated polyps; prognosis improves when coexisting with MSI [56].

Transcriptomic analysis has led to the classification of CRC into four consensus molecular subtypes (CMS): CMS1 (MSI-Immune, 14%), CMS2 (Canonical, 37%), CMS3 (Metabolic, 13%), and CMS4 (Mesenchymal, 23%) [57]. These subtypes differ in mutational patterns, immune activity, and therapeutic response, though clinical translation of CMS classification is still under investigation.

V. COLORECTAL CANCER DEVELOPMENT

Colorectal cancer (CRC) is marked by significant genetic heterogeneity, progressing through multiple molecular pathways and exhibiting a high tumor mutational burden [58]. Based on mutation rates, CRCs are classified as hypermutated (>12 mutations per 10^6 bases) or non-hypermutated (<8.24 mutations per 10^6 bases). The disease arises from sequential genetic and epigenetic changes in colonic epithelial cells, leading to hyperproliferation and tumor formation [59]. Colorectal carcinogenesis occurs primarily via three molecular pathways: microsatellite instability (MSI), chromosomal instability (CIN), and the serrated neoplasia pathway [60,61,62]. The adenoma-carcinoma sequence, typically linked with CIN, is the most common, while serrated neoplasia (10–15% of cases) involves progression from hyperplastic polyps to sessile serrated adenomas and CIMP-high tumors. Chronic inflammation-driven CRC, often in colitis patients, accounts for less than 2% of cases [63].

CRC usually takes around 18 years to progress from polyp to carcinoma, with metastasis developing in about 9 years [64]. Adenocarcinomas make up 96% of cases and are staged from 0 to IV, based on invasion and spread [65]. Treatment varies by stage, from surgery alone (Stages 0–II) to chemotherapy (Stage III) and multimodal approaches for metastatic disease (Stage IV) [66]. Despite current treatments, metastatic CRC remains largely incurable, demanding ongoing therapeutic research.

VI. RISK FACTORS

Personal and Medical History

Non-modifiable CRC risk factors include age (most cases occur after 50, peaking at 63–72 years), male sex (30% higher incidence than women), and racial/medical history. Steele et al. found 77% of cases occur in adults aged 60–89 [67,68,69]. Early-onset CRC (18–49 years) disproportionately affects men (OR 1.87), Black (OR 1.73), and Asian (OR 2.60) individuals, and those with IBD [70]. Men also face higher rectal cancer (OR 2.84) [71]. Racial disparities exist, with Black individuals having the highest incidence and mortality, particularly for proximal (OR 1.62) and distal (OR 1.27) colon cancer, though slightly lower rectal cancer risk (OR 0.88) versus Whites [72,73].

Chronic Conditions and CRC Risk

Chronic illnesses like IBD (ulcerative colitis or Crohn's disease) increase CRC risk nearly threefold [74,75]. Type 2 diabetes also raises CRC risk, especially for proximal colon cancer (OR 1.29), with even higher associations reported in African populations (OR 5.3) [76]. Mechanistically, hyperinsulinemia enhances IGF-1 activity, promoting cell proliferation and DNA damage [77,78].

Family History

A first-degree relative with CRC nearly doubles personal risk (RR 1.80). Risk is especially high for early-onset cases (RR 8.61), who are also more likely to report familial CRC history (RR 2.87). Korean studies show increased distal colon cancer risk for both sexes (HR 1.8) and a male-specific rise in proximal tumors (HR 2.4) [79].

Two key inherited syndromes are:

- FAP, caused by APC mutations, leading to extensive polyps and near-universal malignancy without intervention [80,81].

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- Lynch Syndrome, linked to mismatch repair gene mutations, carries over a 60% lifetime CRC risk, often presenting by age 45 [82].

Lifestyle and Dietary Intake

Obesity increases CRC risk by 10% per 8 kg/m² BMI, especially in men. Physical activity lowers risk and enhances survival [83,84]. CRC risk escalates with higher alcohol intake, showing a dose-response relationship. Rectal cancer exhibits particular susceptibility, with chronic consumption elevating risk approximately twofold [85,86,87,88]. Nicotine exposure confers elevated rectal cancer risk (odds ratio 1.81) via EGFR activation and angiogenic pathway induction [89,90]. Red and processed meats raise CRC risk by 20–30% (RR 1.13), due to carcinogens like heme iron and HCAs, while white meat shows no such link [91,92]. Protective dietary elements include high fiber (14% risk reduction), vitamin D, calcium, and a diet rich in fruits, vegetables, and whole grains [93,94,95,96].

Medication and Hormones

Regular use of aspirin or NSAIDs can reduce CRC risk by 20–40%, particularly for rectal cancer (OR 0.71), though risks like GI bleeding (OR 1.8) and heart events (HR 1.3) limit general recommendations [97].
Hormone therapy (HT) after menopause is linked to reduced CRC risk (RR 0.61), with combination therapy (RR 0.85) more protective than estrogen alone (RR 0.91). Post-diagnosis HT use is associated with reduced CRC-specific (26%) and all-cause mortality (30%) [98].

VII. PREVENTIVE STRATEGIES

Molecular Mechanisms and Gut Microbiota

Dietary habits and gastrointestinal microbial communities play significant roles in CRC pathogenesis. While the precise molecular pathways remain unclear, imbalanced gut microbiota—often shaped by diet—may contribute to CRC initiation and progression [99,100]. Modulating microbial composition presents therapeutic opportunities, potentially enhancing treatment outcomes and minimizing side effects [101]. However, challenges in CRC pathogenesis, diagnosis, and therapy call for continued research.

Primary Prevention

Primary prevention aims to reduce CRC risk in healthy populations. Sustained efforts to lower modifiable risk factors may significantly decrease CRC incidence and mortality over time [102]. Key interventions involve smoking reduction [103], moderate drinking [104], obesity control [105], and reduced intake of cured/red meats [106]. Protective actions include regular physical activity [107], aspirin use [108,109], and hormone replacement therapy [110]. Diets high in milk and whole grains may offer additional protection.

Secondary Prevention

Due to CRC's slow progression, early detection through colonoscopy is effective in preventing invasive cancer [111]. Alternative screening methods include sigmoidoscopy and stool-based tests like FOBT. Emerging modalities, including capsule endoscopy, CT colonography, stool DNA analysis, and liquid biopsies, show potential but face constraints regarding expense and diagnostic accuracy.Investigations of blood-derived omics signatures show promise for improving CRC detection methods [112].

Tertiary Prevention

Lifestyle factors like smoking and alcohol use negatively impact CRC survival due to treatment complications and biological tumor-promoting effects [113,114,115,116,117,118]. In contrast, physical activity improves survival by enhancing metabolic and immune functions [119,120,121,122,123], especially in non-metastatic cases [124], with limited data in metastatic disease [125]. Chemoprevention with low-dose aspirin [126,127,128] and possibly metformin [129] shows promise, while beta-blockers lack benefit [130]. Vitamin D supplementation may improve survival, particularly in metastatic CRC, though more trials are needed [131,132,133,134,135,136].

VIII. DIAGNOSIS

Clinical Presentation

Widespread use of colonoscopic screening has enabled early detection of most colorectal cancers (CRC), often before symptoms appear. Symptom profiles differ according to the lesion's site and extent within the colon. The most frequent indications for diagnostic colonoscopy are hematochezia (37%), abdominal discomfort (34%), and iron-deficiency anemia of unknown origin (23%).Right-sided tumors typically cause iron deficiency anemia, while left-sided lesions often result in altered bowel habits, such as constipation or stool narrowing. Acute presentations may

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include intestinal occlusion, visceral perforation, or significant hemorrhage requiring emergent intervention. Advanced disease may lead to metastatic symptoms like jaundice, bone pain, or respiratory distress.

Physical Examination

Physical assessment is vital, focusing on signs of metastasis. Abdominal exams should evaluate for tenderness, masses, or organ enlargement. Digital rectal examination (DRE) is indispensable for identifying rectal abnormalities and evaluating anal sphincter function [137].

Diagnostic Testing

Initial imaging may include a barium enema or CT colonography, but colonoscopy with biopsy remains the diagnostic gold standard, with ~94.7% sensitivity (95% CI: 90%-97%) when properly conducted. Multiple specimen collections with site marking aid in delineating surgical margins and resection planning.Laboratory workup includes CBC, iron studies, liver and kidney function tests, coagulation profile, and carcinoembryonic antigen (CEA) levels for prognosis and monitoring.

Molecular and Imaging Assessment

NCCN recommends universal testing for mismatch repair (MMR) or microsatellite instability (MSI), especially in sporadic CRC cases (15–20%). For metastatic CRC, KRAS, NRAS, BRAF, and HER2 mutation testing informs therapy. The standard staging protocol mandates thoracic, abdominal, and pelvic CT evaluation. MRI is used for liver metastases or contrast allergies; PET-CT is not routine [138].

Additional Diagnostic Considerations

FIT or FOBT are screening tools requiring a follow-up colonoscopy if positive. Flexible sigmoidoscopy identifies left-sided tumors but is incomplete. Germline genetic evaluation should be considered for early-onset cases and individuals with hereditary cancer predisposition. Endoscopic ultrasound assists rectal tumor staging, while liquid biopsy is emerging for mutation tracking and response monitoring [139].

IX. TREATMENT

Surgery and Chemotherapy

The cornerstone of colorectal cancer management continues to be surgical resection combined with systemic chemotherapy.However, metastatic CRC remains challenging, as 25% of patients are diagnosed at advanced stages, and 20% later develop metastases. Surgery is critical for localized disease, while chemotherapy or radiotherapy is often required pre- or post-operatively [140]. Chemotherapeutic options include single-agent 5-FU or combination regimens such as FOLFOX, FOLFIRI, XELOX/CAPOX, and CAPIRI. While similarly effective, these combinations vary in toxicity, and single agents are reserved for patients with lower tolerance [141]. Resistance, systemic toxicity, and lack of specificity underscore the need for improved therapies.

Targeted Therapy

Monoclonal antibodies targeting EGFR (cetuximab) and VEGF (bevacizumab) have significantly enhanced survival outcomes in colorectal cancer patients. New agents are being developed to target multiple signaling pathways (VEGF/VEGFR, EGFR, HGF/c-MET, IGF-1R, TGF-β, Wnt, Notch, Hedgehog) [142]. Nanotechnology offers improved drug delivery using colon-specific carriers and theranostic nanoparticles that enable simultaneous therapy and diagnostics.

Gene Therapy

Gene therapy addresses CRC by correcting mutations in oncogenes or tumor suppressors via RNA/DNA vectors [143]. As of 2017, over 2,600 gene therapy trials were registered globally, but only 45 reached Phase III, reflecting translational challenges. In the UK, 11 trials targeted CRC specifically [144,145]. Gene therapy holds promise for precise targeting and halting tumor growth [146].

Immunotherapy

Immunotherapy aims to enhance immune responses against CRC using monoclonal antibodies, checkpoint inhibitors, cancer vaccines, adoptive T-cell transfer, complement inhibition, and cytokines [147]. Though many trials are early-stage, results are promising, with 24 completed and 40+ ongoing [148].

Monoclonal Antibody Therapy

Cetuximab and panitumumab target EGFR in metastatic CRC. Emerging immunotherapeutic antibodies targeting EpCAM (adecatumumab), CEA (labetuzumab), and mucin antigens (pemtumomab) are broadening CRC treatment possibilities [149].

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Immune Checkpoint Inhibitor Therapy

Checkpoint inhibitors such as Nivolumab (anti-PD-1) and Ipilimumab (anti-CTLA-4) aim to reactivate T-cells by blocking tumor-induced immune suppression, showing promise in clinical trials [150].

Cancer Vaccines

Cancer vaccines stimulate dendritic cells (DCs) to activate antigen-specific immune responses. OncoVAX and DC-based vaccines are leading candidates for CRC treatment [151].

DC Vaccine

Vaccines using CEA-derived peptides or mRNA successfully induce cytotoxic T-cell responses in metastatic CRC, supporting their therapeutic potential [152].

OncoVAX

OncoVAX combines autologous tumor cells with adjuvants to prevent recurrence. It has shown improved survival when paired with surgery in colon cancer patients [153,154].

Adoptive T-Cell Therapy

Adoptive T-cell therapy, including CAR-T and Vδ1 γδ T-cells, offers tumor-specific cytotoxicity. Preclinical studies in CRC xenograft models show strong efficacy [155].

Complement Inhibition

Complement inhibitors such as CVF and protein A enhance anti-tumor immunity and suppress tumor-related immune evasion, effective alone or with other therapies [156].

Cytokine Therapy

Pro-inflammatory cytokines (TNF-α, IL-6) stimulate NF-κB and STAT3 signaling pathways, driving colorectal carcinoma proliferation.Targeting these pathways via cytokine therapy may inhibit tumor progression [157].

Natural Products as Therapy

Natural compounds, relied upon by 75–80% of the global population, offer multi-target cancer effects [158,159]. Nearly half of approved cancer drugs originate from natural sources like polyphenols and alkaloids [160,161,162]. Clinical trials support phytochemicals (curcumin, resveratrol, berberine, metformin) for anti-cancer effects [163,164]. Combining them with chemotherapy enhances efficacy. Chinese pharmacopeia-registered botanicals (Ai-Di/Matrine) demonstrate both therapeutic enhancement and toxicity mitigation when combined with FOLFOX regimens [165].Additionally, dietary herbs and spices modulate cancer-related pathways (e.g., BCL-2, K-ras, MMPs, caspases), offering chemopreventive potential [166,167].

X. RECOMMENDATIONS

The global incidence and mortality of colorectal cancer (CRC) are expected to rise markedly due to aging populations and increasing modifiable risk factors such as poor diet, obesity, and sedentary lifestyles. Without robust prevention strategies, this trend will likely worsen. Primary prevention targeting shared risk factors with other chronic diseases offers long-term benefits, though outcomes require extended evaluation. Secondary prevention through cost-effective screening (e.g., fecal tests, sigmoidoscopy, colonoscopy) can significantly reduce CRC mortality within 10–20 years. Emerging noninvasive diagnostics, like blood-based omic biomarkers, may further enhance early detection. Tertiary prevention strategies—such as aspirin use, smoking cessation, and physical activity—can improve outcomes for diagnosed individuals.

A comprehensive CRC control plan should include:

1. Lifestyle interventions promoting exercise, healthy diets, and weight control;
2. Strengthened screening infrastructure with quality monitoring;
3. Investment in noninvasive diagnostics and personalized treatments;
4. Integration of tertiary prevention in survivorship care;
5. Public education on risks and screenings;
6. Policies enhancing access to care;
7. Promotion of chemopreventive herbs and spices;
8. Stronger health systems for equitable care access.

A combined primary, secondary, and tertiary prevention approach, particularly one that integrates dietary strategies, is key to reducing CRC burden and improving patient outcomes.

XI. CONCLUSIONS

Addressing the growing colorectal cancer (CRC) burden requires an integrated strategy focusing on reducing modifiable risk factors, advancing chemoprevention research, and implementing population-tailored screening programs. Public education should highlight CRC

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risks and promote protective dietary habits, including fruits, herbs, and spices. Regional healthcare capacities must guide strategy execution to ensure impact and feasibility. Research into polymer-based nanocarrier drug delivery is a promising therapeutic direction. A coordinated, evidence-based approach—combining public health efforts, personalized prevention, and innovative treatments—can significantly reduce CRC incidence and mortality, provided there is strong commitment from policymakers, clinicians, scientists, and communities.

ABBREVIATIONS USED

- **APC -** Adenomatous Polyposis Coli (gene)
- **ASMR -** Age-Standardized Mortality Rate
- **ASR -** Age-Standardized Rate
- **IBD -** Inflammatory Bowel Disease
- **IGF -** Insulin-like Growth Factor
- **IRI -** Irinotecan
- **MAPK -** Mitogen-Activated Protein Kinase
- **MMR -** Mismatch Repair
- **MSI** - Microsatellite Instability
- **mTOR -** Mechanistic Target of Rapamycin
- **NF-κB -** Nuclear Factor Kappa B
- **NSAIDs -** Non-Steroidal Anti-Inflammatory Drugs
- **OR -** Odds Ratio
- **OX -** Oxaliplatin
- **PAHs -** Polycyclic Aromatic Hydrocarbons
- **PD-1 -** Programmed Death-1 (receptor)
- **PD-L1/PD-L2 -** Programmed Death-Ligand 1/2
- **PDENs -** Polymer-Drug Encapsulated Nanoparticles
- **PI3K -** Phosphoinositide 3-Kinase
- **PMS2 -** Post-Meiotic Segregation Increased 2 (gene)
- **RAS -** Rat Sarcoma (gene family)
- **RR -** Relative Risk
- **STAT3 -** Signal Transducer and Activator of Transcription 3
- **T2DM -** Type 2 Diabetes Mellitus
- **TGF-β -** Transforming Growth Factor Beta
- **TNF -** Tumor Necrosis Factor
- **VEGF/VEGFR -** Vascular Endothelial Growth Factor/Receptor
- **WNT -** Wingless-Type (signaling pathway)

REFERENCES

[1]. WHO Cancer. [(accessed on 14 July 2021)]. Available online: https://www.who.int/news-room/fact-sheets/detail/cancer.

[2]. Hossain, M. S., Karuniawati, H., Jairoun, A. A., Urbi, Z., Ooi, D. J., John, A., Lim, Y. C., Kibria, K. M. K., Mohiuddin, A. M., Ming, L. C., Goh, K. W., & Hadi, M. A. (2022). Colorectal Cancer: A review of carcinogenesis, global epidemiology, current challenges, risk factors, preventive and treatment strategies. Cancers, 14(7), 1732. https://doi.org/10.3390/cancers14071732.

[3]. Ferlay J., Ervik M., Lam F., Colombet M., Mery L., Piñeros M., Znaor A., Soerjomataram I., Bray F. Global Cancer Observatory: Cancer Today. [(accessed on 14 July 2021)]. Available online: https://gco.iarc.fr/today.

[4]. Papamichael, D., Audisio, R., Glimelius, B., De Gramont, A., Glynne-Jones, R., Haller, D., Köhne, C., Rostoft, S., Lemmens, V., Mitry, E., Rutten, H., Sargent, D., Sastre, J., Seymour, M., Starling, N., Van Cutsem, E., & Aapro, M. (2014). Treatment of colorectal cancer in older patients: International Society of Geriatric Oncology (SIOG) consensus recommendations 2013. Annals of Oncology, 26(3), 463–476. https://doi.org/10.1093/annonc/mdu253.

[5]. Douaiher, J., Ravipati, A., Grams, B., Chowdhury, S., Alatise, O., & Are, C. (2017). Colorectal cancer—global burden, trends, and geographical variations. Journal of Surgical Oncology, 115(5), 619–630. https://doi.org/10.1002/jso.24578.

[6]. Sawicki, T., Ruszkowska, M., Danielewicz, A., Niedźwiedzka, E., Arłukowicz, T., &Przybyłowicz, K. E. (2021). A review of colorectal cancer in terms of epidemiology, risk factors, development, symptoms and diagnosis. Cancers, 13(9), 2025. https://doi.org/10.3390/cancers13092025.

[7]. Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA a Cancer Journal for Clinicians, 68(6), 394–424. https://doi.org/10.3322/caac.21492.

[8]. Arnold, M., Sierra, M. S., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2016). Global patterns and trends in

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May-June 2025, pp: 1933-1950 www.ijprajournal.com ISSN: 2456-4494

colorectal cancer incidence and mortality. Gut, 66(4), 683–691. https://doi.org/10.1136/gutjnl-2015-310912.

[9]. World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) Continuous Update Project Report: Diet, Nutrition, Physical Activity and Colorectal Cancer 2016. World Cancer Research Fund International; London, UK: 2018.

[10]. Murphy, N., Moreno, V., Hughes, D. J., Vodicka, L., Vodicka, P., Aglago, E. K., Gunter, M. J., & Jenab, M. (2019). Lifestyle and dietary environmental factors in colorectal cancer susceptibility. Molecular Aspects of Medicine, 69, 2–9. https://doi.org/10.1016/j.mam.2019.06.005.

[11]. Zaytseva, Y. (2021). Lipid metabolism as a targetable metabolic vulnerability in colorectal cancer. Cancers, 13(2), 301. https://doi.org/10.3390/cancers13020301.

[12]. Triantafillidis JK, Nasioulas G, Kosmidis PA. Colorectal cancer and inflammatory bowel disease: epidemiology, risk factors, mechanisms of carcinogenesis and prevention strategies. Anticancer Res. 2009 Jul;29(7):2727-37. PMID: 19596953.

[13]. Edwards, B. K., Ward, E., Kohler, B. A., Eheman, C., Zauber, A. G., Anderson, R. N., Jemal, A., Schymura, M. J., Lansdorp- Vogelaar, I., Seeff, L. C., Van Ballegooijen, M., Goede, S. L., & Ries, L. a. G. (2009). Annual report to the nation on the status of cancer, 1975- 2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. Cancer, 116(3), 544–573. https://doi.org/10.1002/cncr.24760.

[14]. Navarro, M., Nicolas, A., Ferrandez, A., & Lanas, A. (2017). Colorectal cancer population screening programs worldwide in 2016: An update. World Journal of Gastroenterology, 23(20), 3632. https://doi.org/10.3748/wjg.v23.i20.3632.

[15]. Wilson JM, Jungner YG. Principios y metodos del examen colectivo para identificarenfermedades [Principles and practice of mass screening for disease]. Bol Oficina Sanit Panam. 1968 Oct;65(4):281-393. Spanish. PMID: 4234760.

[16]. Morson, B. (1984). The evolution of colorectal carcinoma. Clinical Radiology, 35(6), 425–431. https://doi.org/10.1016/s0009-9260(84)80033-1.

[17]. Winawer, S., Fletcher, R., Miller, L., Godlee, F., Stolar, M., Mulrow, C., Woolf, S., Glick, S., Ganiats, T., Bond, J., Rosen, L., Zapka, J., Olsen, S., Giardiello, F., Sisk, J., Van Antwerp, R., Brown-Davis, C., Marciniak, D., & Mayer, R. (1997). Colorectal cancer screening: Clinical guidelines and rationale. Gastroenterology, 112(2), 594–642. https://doi.org/10.1053/gast.1997.v112.agast970594.

[18]. Winawer, S. J., Zauber, A. G., Ho, M. N., O'Brien, M. J., Gottlieb, L. S., Sternberg, S. S., Waye, J. D., Schapiro, M., Bond, J. H., Panish, J. F., Ackroyd, F., Shike, M., Kurtz, R. C., Hornsby-Lewis, L., Gerdes, H., & Stewart, E. T. (1993). Prevention of colorectal cancer by colonoscopic polypectomy. New England Journal of Medicine, 329(27), 1977–1981. https://doi.org/10.1056/nejm199312303292701.

[19]. Ciccolallo, L., Capocaccia, R., Coleman, M. P., Berrino, F., Coebergh, J. W. W., Damhuis, R. a. M., Faivre, J., Martinez-Garcia, C., Møller, H., De Leon, M. P., Launoy, G., Raverdy, N., Williams, E. M. I., & Gatta, G. (2005). Survival differences between European and US patients with colorectal cancer: role of stage at diagnosis and surgery. Gut, 54(2), 268–273. https://doi.org/10.1136/gut.2004.044214.

[20]. Garcia-Etxebarria, K., Clos-Garcia, M., Telleria, O., Nafría, B., Alonso, C., Iruarrizaga-Lejarreta, M., Franke, A., Crespo, A., Iglesias, A., Cubiella, J., Bujanda, L., & Falcón-Pérez, J. (2021). Interplay between Genome, Metabolome and Microbiome in Colorectal Cancer. Cancers, 13(24), 6216. https://doi.org/10.3390/cancers13246216.

[21]. Keum, N., & Giovannucci, E. (2019). Global burden of colorectal cancer: emerging trends, risk factors and prevention strategies. Nature Reviews Gastroenterology & Hepatology, 16(12), 713–

732. https://doi.org/10.1038/s41575-019-0189-8.

[22]. ACS Cancer Facts & Figures. 2020. [(accessed on 15 July 2021)]. Available online: https://www.cancer.org/cancer/colon-rectal-cancer/.

[23]. Ferlay J., Ervik M., Lam F., Colombet M., Mery L., Piñeros M., Znaor A., Soerjomataram I., Bray F. Global Cancer Observatory: Cancer Today. [(accessed on 10 October 2023)]. Available online: https://gco.iarc.fr/today.

[24]. Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA a Cancer Journal for Clinicians, 71(3), 209–249. https://doi.org/10.3322/caac.21660.

[25]. Roshandel, G., Ghasemi-Kebria, F., & Malekzadeh, R. (2024). Colorectal cancer: epidemiology, risk factors, and prevention. Cancers, 16(8), 1530. https://doi.org/10.3390/cancers16081530.

[26]. Ervik M., Lam F., Laversanne M., Ferlay J., Bray F. Global Cancer Observatory: Cancer Over Time. [(accessed on 23 March 2023)]. Available online: https://gco.iarc.fr/overtime

[27]. Siegel, R. L., Miller, K. D., Sauer, A. G., Fedewa, S. A., Butterly, L. F., Anderson, J. C., Cercek, A., Smith, R. A., & Jemal, A. (2020). Colorectal cancer statistics, 2020. CA a Cancer Journal for Clinicians, 70(3), 145–164. https://doi.org/10.3322/caac.21601.

[28]. Bray F. Transitions in human development and the global cancer burden. In: Stewart B.W., Wild C.P., editors. World Cancer Report. Volume 34. WHO Press; Geneva, Switzerland: 2014. pp. 42–55.

[29]. Fidler, M. M., Soerjomataram, I., & Bray, F. (2016). A global view on cancer incidence and national levels of the human development index. International Journal of Cancer, 139(11), 2436–2446. https://doi.org/10.1002/ijc.30382.

[30]. Arnold, M., Abnet, C. C., Neale, R. E., Vignat, J., Giovannucci, E. L., McGlynn, K. A., & Bray, F. (2020). Global burden of 5 major types of gastrointestinal cancer. Gastroenterology, 159(1), 335-349.e15. https://doi.org/10.1053/j.gastro.2020.02.068.

[31]. Safiri, S., Sepanlou, S. G., Ikuta, K. S., Bisignano, C., Salimzadeh, H., Delavari, A., Ansari, R., Roshandel, G., Merat, S., Fitzmaurice, C., Force, L. M., Nixon, M. R., Abbastabar, H., Abegaz, K. H., Afarideh, M., Ahmadi, A., Ahmed, M. B., Akinyemiju, T., Alahdab, F., . . . Malekzadeh, R. (2019). The global, regional, and national burden of colorectal cancer and its attributable risk factors in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. Gastroenterology & Hepatology, 4(12), 913–933. https://doi.org/10.1016/s2468-1253(19)30345-0.

[32]. Ferlay J., Laversanne M., Ervik M., Lam F., Colombet M., Mery L., Piñeros M., Znaor A., Soerjomataram I., Bray F. Global Cancer Observatory: Cancer Tomorrow. [(accessed on 10 October 2023)]. Available online: https://gco.iarc.fr/tomorrow.

[33]. Brenner, D. R., Heer, E., Sutherland, R. L., Ruan, Y., Tinmouth, J., Heitman, S. J., &Hilsden, R. J. (2019). National trends in colorectal cancer incidence among older and younger adults in Canada. JAMA Network Open, 2(7), e198090. https://doi.org/10.1001/jamanetworkopen.2019.8090.

[34]. Abualkhair, W. H., Zhou, M., Ahnen, D., Yu, Q., Wu, X., &Karlitz, J. J. (2020). Trends in incidence of Early-Onset Colorectal cancer in the United States among those approaching screening age. JAMA Network Open, 3(1), e1920407. https://doi.org/10.1001/jamanetworkopen.2019.20407.

[35]. Meester, R. G. S., Mannalithara, A., Lansdorp-Vogelaar, I., &Ladabaum, U. (2019). Trends in incidence and stage at diagnosis of colorectal cancer in adults aged 40 through 49 years, 1975-2015. JAMA, 321(19), 1933. https://doi.org/10.1001/jama.2019.3076.

[36]. Ward, E. M., Sherman, R. L., Henley, S. J., Jemal, A., Siegel, D. A., Feuer, E. J., Firth, A. U., Kohler, B. A., Scott, S., Ma, J., Anderson, R. N., Benard, V., & Cronin, K. A. (2019). Annual Report to the Nation on the status of Cancer, featuring cancer in men and women age 20–49 years. JNCI Journal of the National Cancer Institute, 111(12),

1279–1297. https://doi.org/10.1093/jnci/djz106.

[37]. Montminy, E. M., Zhou, M., Maniscalco, L., Abualkhair, W., Kim, M. K., Siegel, R. L., Wu, X., Itzkowitz, S. H., &Karlitz, J. J. (2020). Contributions of adenocarcinoma and carcinoid tumors to Early-Onset Colorectal Cancer incidence rates in the United States. Annals of Internal Medicine, 174(2), 157–166. https://doi.org/10.7326/m20-0068.

[38]. Howren, A., Sayre, E. C., Loree, J. M., Gill, S., Brown, C. J., Raval, M. J., Farooq, A., & De Vera, M. A. (2021). Trends in the incidence of young-onset colorectal cancer with a focus on years approaching screening age: A population-based longitudinal study. JNCI Journal of the National Cancer Institute. https://doi.org/10.1093/jnci/djaa220.

[39]. Bailey, C. E., Hu, C., You, Y. N., Bednarski, B. K., Rodriguez-Bigas, M. A., Skibber, J. M., Cantor, S. B., & Chang, G. J. (2014). Increasing Disparities in the Age-Related Incidences of Colon and Rectal Cancers in the United States, 1975-2010. JAMA Surgery, 150(1), 17. https://doi.org/10.1001/jamasurg.2014.1756.

[40]. Emile, S. H., Horesh, N., Freund, M. R., Garoufalia, Z., Gefen, R., Silva-Alvarenga, E., Maron, D. J., DaSilva, G., & Wexner, S. D. (2022). Trends in the characteristics, treatment, and outcomes of rectal adenocarcinoma in the US from 2004 to 2019. JAMA Oncology, 9(3), 355. https://doi.org/10.1001/jamaoncol.2022.6116.

[41]. Mork, M. E., You, Y. N., Ying, J., Bannon, S. A., Lynch, P. M., Rodriguez-Bigas, M. A., & Vilar, E. (2015). High prevalence of hereditary cancer syndromes in adolescents and young adults with colorectal cancer. Journal of Clinical Oncology, 33(31), 3544–3549. https://doi.org/10.1200/jco.2015.61.4503.

[42]. Chang, D. T., Pai, R. K., Rybicki, L. A., Dimaio, M. A., Limaye, M., Jayachandran, P., Koong, A. C., Kunz, P. A., Fisher, G. A., Ford, J. M., Welton, M., Shelton, A., Ma, L., Arber, D. A., & Pai, R. K. (2012). Clinicopathologic and molecular features of sporadic early-onset colorectal adenocarcinoma: an adenocarcinoma with frequent signet ring cell differentiation, rectal and sigmoid involvement, and adverse morphologic features. Modern Pathology, 25(8), 1128–1139. https://doi.org/10.1038/modpathol.2012.61.

[43]. Murphy, N., Campbell, P. T., & Gunter, M. J. (2020). Unraveling the etiology of Early-Onset colorectal cancer. JNCI Journal of the National Cancer Institute, 113(5), 505–506. https://doi.org/10.1093/jnci/djaa165.

[44]. Cercek, A., Chatila, W. K., Yaeger, R., Walch, H., Fernandes, G. D. S., Krishnan, A., Palmaira, L., Maio, A., Kemel, Y., Srinivasan, P., Bandlamudi, C., Salo-Mullen, E., Tejada, P. R., Belanfanti, K., Galle, J., Joseph, V., Segal, N., Varghese, A., Reidy-Lagunes, D., . . . Stadler, Z. K. (2021). A comprehensive comparison of Early-Onset and Average-Onset colorectal cancers. JNCI Journal of the National Cancer Institute, 113(12), 1683–1692. https://doi.org/10.1093/jnci/djab124.

[45]. Ahnen, D. J., Wade, S. W., Jones, W. F., Sifri, R., Silveiras, J. M., Greenamyer, J., Guiffre, S., Axilbund, J., Spiegel, A., & You, Y. N. (2014). The increasing incidence of Young-Onset Colorectal Cancer: a call to action. Mayo Clinic Proceedings, 89(2), 216–224. https://doi.org/10.1016/j.mayocp.2013.09.006.

[46]. Wu, S., Wang, H., Li, Y., Xie, Y., Huang, C., Zhao, H., Miyagishi, M., & Kasim, V. (2018). Transcription factor YY1 promotes cell proliferation by directly activating the pentose phosphate pathway. Cancer Research, 78(16), 4549–4562. https://doi.org/10.1158/0008-5472.can-17-4047.

[47]. Yang, Y., Du, L., Shi, D., Kong, C., Liu, J., Liu, G., Li, X., & Ma, Y. (2021). Dysbiosis of human gut microbiome in young-onset colorectal cancer. Nature Communications, 12(1). https://doi.org/10.1038/s41467-021-27112-y.

[48]. Allen, J., & Sears, C. L. (2019). Impact of the gut microbiome on the genome and epigenome of colon epithelial cells: contributions to colorectal cancer development. Genome Medicine, 11(1). https://doi.org/10.1186/s13073-019-0621-2

[49]. Snyder, C., & Hampel, H. (2019). Hereditary colorectal cancer syndromes. Seminars in Oncology Nursing, 35(1), 58–

78. https://doi.org/10.1016/j.soncn.2018.12.011

[50]. Birch, R. J., Burr, N., Subramanian, V., Tiernan, J. P., Hull, M. A., Finan, P., Rose, A., Rutter, M., Valori, R., Downing, A., & Morris, E. J. (2022). Inflammatory Bowel Disease-Associated Colorectal Cancer Epidemiology and Outcomes: An English Population-Based Study. The American Journal of Gastroenterology, 117(11), 1858–1870. https://doi.org/10.14309/ajg.0000000000001941

[51]. Loh, N. Y., Wang, W., Noordam, R., & Christodoulides, C. (2022). Obesity, fat distribution and risk of cancer in women and men: a Mendelian randomisation study. Nutrients, 14(24), 5259. https://doi.org/10.3390/nu14245259

[52]. Lu, L., Mullins, C. S., Schafmayer, C., Zeißig, S., &Linnebacher, M. (2021). A global assessment of recent trends in gastrointestinal cancer and lifestyle- associated risk factors. Cancer Communications, 41(11), 1137–1151. https://doi.org/10.1002/cac2.12220

[53]. Menon G, Cagir B. Colon Cancer. [Updated 2025 Feb 27]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470380/

[54]. Worthley DL, Leggett BA. Colorectal cancer: molecular features and clinical opportunities. Clin Biochem Rev. 2010 May;31(2):31-8.PMID: 20498827; PMCID: PMC2874430.

[55]. Mármol, I., Sánchez-De-Diego, C., Dieste, A. P., Cerrada, E., &Yoldi, M. R. (2017). Colorectal Carcinoma: A General Overview and future Perspectives in colorectal cancer. International Journal of Molecular Sciences, 18(1), 197. https://doi.org/10.3390/ijms18010197

[56]. Huang, J., Soupir, A. C., Schlick, B. D., Teng, M., Sahin, I. H., Permuth, J. B., Siegel, E. M., Manley, B. J., Pellini, B., & Wang, L. (2021). Cancer detection and classification by CPG Island hypermethylation signatures in plasma Cell-Free DNA. Cancers, 13(22), 5611. https://doi.org/10.3390/cancers13225611.

[57]. Guinney, J., Dienstmann, R., Wang, X., De Reyniès, A., Schlicker, A., Soneson, C., Marisa, L., Roepman, P., Nyamundanda, G., Angelino, P., Bot, B. M., Morris, J. S., Simon, I. M., Gerster, S., Fessler, E., De Sousa E Melo, F., Missiaglia, E., Ramay, H., Barras, D., . . . Tejpar, S. (2015). The consensus molecular subtypes of colorectal cancer. Nature Medicine, 21(11), 1350–1356. https://doi.org/10.1038/nm.3967.

[58]. Comprehensive molecular characterization of human colon and rectal cancer. (2012). Nature, 487(7407), 330–337. https://doi.org/10.1038/nature11252.

[59]. Testa, U., Pelosi, E., & Castelli, G. (2018). Colorectal cancer: genetic abnormalities, tumor progression, tumor heterogeneity, clonal evolution and Tumor-Initiating cells. Medical Sciences, 6(2), 31. https://doi.org/10.3390/medsci6020031.

[60]. Malki, A., ElRuz, R. A., Gupta, I., Allouch, A., Vranic, S., & Moustafa, A. A. (2020). Molecular mechanisms of colon cancer progression and metastasis: recent insights and advancements. International Journal of Molecular Sciences, 22(1), 130. https://doi.org/10.3390/ijms22010130.

[61]. Nguyen, H., & Duong, H. (2018). The molecular characteristics of colorectal cancer: Implications for diagnosis and therapy (Review). Oncology Letters. https://doi.org/10.3892/ol.2018.8679.

[62]. Vogelstein, B., Fearon, E. R., Hamilton, S. R., Kern, S. E., Preisinger, A. C., Leppert, M., Smits, A. M., & Bos, J. L. (1988). Genetic Alterations during Colorectal-Tumor Development. New England Journal of Medicine, 319(9), 525–532. https://doi.org/10.1056/nejm198809013190901.

[63]. Pickhardt, P. J., Kim, D. H., Pooler, B. D., Hinshaw, J. L., Barlow, D., Jensen, D., Reichelderfer, M., & Cash, B. D. (2013). Assessment of volumetric growth rates of small colorectal polyps with CT colonography: a longitudinal study of natural history. The Lancet Oncology, 14(8), 711–720. https://doi.org/10.1016/s1470-2045(13)70216-x.

[64]. Stryker, S. J., Wolff, B. G., Culp, C. E., Libbe, S. D., Ilstrup, D. M., &MacCarty, R. L. (1987). Natural history of untreated colonic polyps. Gastroenterology, 93(5), 1009–1013. https://doi.org/10.1016/0016-5085(87)90563-4.

[65]. NIH Advances in Colorectal Cancer Research: Stages of Colorectal Cancer. [(accessed on 30 December 2021)]; Available

online: https://www.nih.gov/research-training/advances-colorectal-cancer-research.

[66]. Slattery, M. (1998). Stage of colon cancer at diagnosis: implications for risk factor associations? International Journal of Epidemiology, 27(3), 382–387. https://doi.org/10.1093/ije/27.3.382.

[67]. Driver, J. A., Gaziano, J. M., Gelber, R. P., Lee, I., Buring, J. E., & Kurth, T. (2007). Development of a risk score for colorectal cancer in men. The American Journal of Medicine, 120(3), 257–263. https://doi.org/10.1016/j.amjmed.2006.05.055.

[68]. Steele S.R., Park G.E., Johnson E.K., Martin M.J., Stojadinovic A., Maykel J.A., Causey M.W. The impact of age on colorectal cancer incidence, treatment, and outcomes in an equal-access health care system. Dis. Colon Rectum. 2014;57:303–310. doi: 10.1097/DCR.0b013e3182a586e7.

[69]. Irby K., Anderson W.F., Henson D.E., Devesa S.S. Emerging and widening colorectal carcinoma disparities between Blacks and Whites in the United States (1975–2002) Cancer Epidemiol. Prev. Biomark. 2006;15:792–797. doi: 10.1158/1055-9965.EPI-05-0879.

[70]. Gausman V., Dornblaser D., Anand S., Hayes R.B., O'Connell K., Du M., Liang P.S. Risk Factors Associated With Early-Onset Colorectal Cancer. Clin. Gastroenterol. Hepatol. 2020;18:2752–2759.e2. doi: 10.1016/j.cgh.2019.10.009.

[71]. Demb, J., Earles, A., Martínez, M. E., Bustamante, R., Bryant, A. K., Murphy, J. D., Liu, L., & Gupta, S. (2019). Risk factors for colorectal cancer significantly vary by anatomic site. BMJ Open Gastroenterology, 6(1), e000313. https://doi.org/10.1136/bmjgast-2019-000313.

[72]. Ellis L., Abrahao R., McKinley M., Yang J., Somsouk M., Marchand L.L., Cheng I., Gomez S.L., Shariff-Marco S. Colorectal Cancer Incidence Trends by Age, Stage, and Racial/Ethnic Group in California, 1990–2014. Cancer Epidemiol. Prev. Biomark. 2018;27:1011–1018. doi: 10.1158/1055-9965.EPI-18-0030.

[73]. Thornton J.G., Morris A.M., Thornton J.D., Flowers C.R., McCashland T.M. Racial variation in colorectal polyp and tumor location. J. Natl. Med. Assoc. 2007;99:723-728.

[74]. Peterson Y.C. Risk Factors for Colorectal Cancer. MOJ Surg. 2015;2:37–42. doi: 10.15406/mojs.2015.02.00015.

[75]. Johnson C.M., Wei C., Ensor J.E., Smolenski D.J., Amos C.I., Levin B., Berry D.A. Meta-analyses of colorectal cancer risk factors. Cancer Causes Control. 2013;24:1207–1222. doi: 10.1007/s10552-013-0201-5.

[76]. Katsidzira, L., Gangaidzo, I. T., Makunike-Mutasa, R., Manyanga, T., Matsena-Zingoni, Z., Thomson, S., Matenga, J. A., Rusakaniko, S., & Ramesar, R. (2018). A case–control study of risk factors for colorectal cancer in an African population. European Journal of Cancer Prevention, 28(3), 145–150. https://doi.org/10.1097/cej.0000000000000439.

[77]. Avgerinos K.I., Spyrou N., Mantzoros C.S., Dalamaga M. Obesity and cancer risk: Emerging biological mechanisms and perspectives. Metabolism. 2019;92:121–135. doi: 10.1016/j.metabol.2018.11.001.

[78]. Moschos, S. J., &Mantzoros, C. S. (2002). The role of the IGF system in Cancer: From basic to clinical studies and clinical applications. Oncology, 63(4), 317–332. https://doi.org/10.1159/000066230.

[79]. Shin A., Joo J., Bak J., Yang H.R., Kim J., Park S., Nam B.H. Site-specific risk factors for colorectal cancer in a Korean population. PLoS ONE. 2011;6:e23196. doi: 10.1371/journal.pone.0023196.

[80]. ACS Colorectal Cancer Facts & Figure 2017, Figure 2018 and Figure 2019. [(accessed on 15 September 2021)]. Available online: https://www.cancer.org/content/dam/cancer-org/research/.

[81]. Samadder N.J., Jasperson K., Burt R.W. Hereditary and common familial colorectal cancer: Evidence for colorectal screening. Dig. Dis. Sci. 2015;60:734–747. doi: 10.1007/s10620-014-3465-z.

[82]. Rasool S., Rasool V., Naqvi T., Ganai B.A., Shah B.A. Genetic unraveling of colorectal cancer. Tumor Biol. 2014;35:5067–5082. doi: 10.1007/s13277-014-1713-7.

[83]. Larson E. Community factors in the development of antibiotic resistance. Annu. Rev. Public Health. 2007;28:435–447. doi:

10.1146/annurev.publhealth.28.021406.144020.

[84]. Wolin, K. Y., Yan, Y., Colditz, G. A., & Lee, I. (2009). Physical activity and colon cancer prevention: a meta-analysis. British Journal of Cancer, 100(4), 611–616. https://doi.org/10.1038/sj.bjc.6604917.

[85]. Fedirko V., Tramacere I., Bagnardi V., Rota M., Scotti L., Islami F., Negri E., Straif K., Romieu I., La Vecchia C., et al. Alcohol drinking and colorectal cancer risk: An overall and dose-response meta-analysis of published studies. Ann. Oncol. Off. J. Eur. Soc. Med. Oncol. 2011;22:1958–1972. doi: 10.1093/annonc/mdq653.

[86]. Lin, T., Chien, W., Hu, J., Tzeng, N., Chung, C., Pu, T., Hsiao, C., & Chen, C. (2020). Risk of colorectal cancer in patients with alcoholism: A nationwide, population-based nested case-control study. PLoS ONE, 15(5), e0232740. https://doi.org/10.1371/journal.pone.0232740.

[87]. Pedersen, A. (2003). Relations between amount and type of alcohol and colon and rectal cancer in a Danish population based cohort study. Gut, 52(6), 861–867. https://doi.org/10.1136/gut.52.6.861.

[88]. Rossi, M., Anwar, M. J., Usman, A., Keshavarzian, A., &Bishehsari, F. (2018). Colorectal Cancer and Alcohol Consumption—Populations to Molecules. Cancers, 10(2), 38. https://doi.org/10.3390/cancers10020038.

[89]. Gram I.T., Park S.Y., Wilkens L.R., Haiman C.A., Le Marchand L. Smoking-Related Risks of Colorectal Cancer by Anatomical Subsite and Sex. Am. J. Epidemiol. 2020;189:543–553. doi: 10.1093/aje/kwaa005.

[90]. Jensen K., Afroze S., Munshi M.K., Guerrier M., Glaser S.S. Mechanisms for nicotine in the development and progression of gastrointestinal cancers. Transl. Gastrointest. Cancer. 2012;1:81–87. doi: 10.3978/j.issn.2224-4778.2011.12.01.

[91]. Aykan, N. F. (2015). Red meat and colorectal cancer. Oncology Reviews. https://doi.org/10.4081/oncol.2015.288.

[92]. Bradbury, K. E., Murphy, N., & Key, T. J. (2019). Diet and colorectal cancer in UK Biobank: a prospective study. International Journal of Epidemiology, 49(1), 246–258. https://doi.org/10.1093/ije/dyz064.

[93]. Garland, C. F., & Gorham, E. D. (2016). Dose-response of serum 25-hydroxyvitamin D in association with risk of colorectal cancer: A meta-analysis. The Journal of Steroid Biochemistry and Molecular Biology, 168, 1–8. https://doi.org/10.1016/j.jsbmb.2016.12.003.

[94]. Ishihara, J., Inoue, M., Iwasaki, M., Sasazuki, S., &Tsugane, S. (2008). Dietary calcium, vitamin D, and the risk of colorectal cancer. American Journal of Clinical Nutrition, 88(6), 1576–1583. https://doi.org/10.3945/ajcn.2008.26195.

[95]. Vallès, X., Alonso, M. H., López-Caleya, J. F., Díez-Obrero, V., Dierssen-Sotos, T., Lope, V., Molina-Barceló, A., Chirlaque, M. D., Jiménez-Moleón, J. J., Tardón, G. F., Castilla, J., Amiano, P., Capelo, R., Castaño-Vinyals, G., Guinó, E., De La Torre, A. J. M., Moreno-Iribas, C., Gómez, B. P., Aragonés, N., . . . Moreno, V. (2018). Colorectal cancer, sun exposure and dietary vitamin D and calcium intake in the MCC-Spain study. Environment International, 121, 428–434. https://doi.org/10.1016/j.envint.2018.09.030.

[96]. Teixeira, M. C. (2014). Primary prevention of colorectal cancer: Myth or reality? World Journal of Gastroenterology, 20(41), 15060. https://doi.org/10.3748/wjg.v20.i41.15060.

[97]. Ji, J., Sundquist, J., & Sundquist, K. (2017). Use of hormone replacement therapy improves the prognosis in patients with colorectal cancer: A population- based study in Sweden. International Journal of Cancer, 142(10), 2003–2010. https://doi.org/10.1002/ijc.31228.

[98]. Botteri, E., Støer, N. C., Sakshaug, S., Graff-Iversen, S., Vangen, S., Hofvind, S., De Lange, T., Bagnardi, V., Ursin, G., &Weiderpass, E. (2017). Menopausal hormone therapy and colorectal cancer: a linkage between nationwide registries in Norway. BMJ Open, 7(11), e017639. https://doi.org/10.1136/bmjopen-2017-017639.

[99]. Wong, S. H., & Yu, J. (2019). Gut microbiota in colorectal cancer: mechanisms of action and clinical applications. Nature Reviews Gastroenterology & Hepatology, 16(11), 690–704. https://doi.org/10.1038/s41575-019-0209-8.

[100]. Leeming, E. R., Johnson, A. J., Spector, T. D., & Roy, C. I. L. (2019). Effect of diet on

the gut Microbiota: Rethinking intervention duration. Nutrients, 11(12), 2862. https://doi.org/10.3390/nu11122862.

[101]. Wong, S. H., & Yu, J. (2019b). Gut microbiota in colorectal cancer: mechanisms of action and clinical applications. Nature Reviews Gastroenterology & Hepatology, 16(11), 690–704. https://doi.org/10.1038/s41575-019-0209-8.

[102]. Cronin, K. A., Krebs-Smith, S. M., Feuer, E. J., Troiano, R. P., & Ballard-Barbash, R. (2001). Evaluating the impact of population changes in diet, physical activity, and weight status on population risk for colon cancer (United States). Cancer Causes & Control, 12(4), 305–316. https://doi.org/10.1023/a:1011244700531.

[103]. Botteri, E., Iodice, S., Bagnardi, V., Raimondi, S., Lowenfels, A. B., & Maisonneuve, P. (2008). Smoking and colorectal cancer. JAMA, 300(23), 2765. https://doi.org/10.1001/jama.2008.839.

[104]. Bagnardi, V., Rota, M., Botteri, E., Tramacere, I., Islami, F., Fedirko, V., Scotti, L., Jenab, M., Turati, F., Pasquali, E., Pelucchi, C., Galeone, C., Bellocco, R., Negri, E., Corrao, G., Boffetta, P., & La Vecchia, C. (2014). Alcohol consumption and site-specific cancer risk: a comprehensive dose–response meta-analysis. British Journal of Cancer, 112(3), 580–593. https://doi.org/10.1038/bjc.2014.579.

[105]. Freisling H., Arnold M., Soerjomataram I., O'Doherty M.G., Ordonez-Mena J.M., Bamia C., Kampman E., Leitzmann M., Romieu I., Kee F., et al. Comparison of general obesity and measures of body fat distribution in older adults in relation to cancer risk: Meta-analysis of individual participant data of seven prospective cohorts in Europe. Br. J. Cancer. 2017;116:1486–1497. doi: 10.1038/bjc.2017.106.

[106]. Vieira, A., Abar, L., Chan, D., Vingeliene, S., Polemiti, E., Stevens, C., Greenwood, D., & Norat, T. (2017). Foods and beverages and colorectal cancer risk: a systematic review and meta-analysis of cohort studies, an update of the evidence of the WCRF-AICR Continuous Update Project. Annals of Oncology, 28(8), 1788–1802. https://doi.org/10.1093/annonc/mdx171.

[107]. Boyle, T., Keegel, T., Bull, F., Heyworth, J., & Fritschi, L. (2012). Physical activity and risks of proximal and distal colon cancers: a systematic review and meta-analysis. JNCI Journal of the National Cancer Institute, 104(20), 1548–1561. https://doi.org/10.1093/jnci/djs354.

[108]. Cao, Y., Nishihara, R., Wu, K., Wang, M., Ogino, S., Willett, W. C., Spiegelman, D., Fuchs, C. S., Giovannucci, E. L., & Chan, A. T. (2016). Population-wide impact of long-term use of aspirin and the risk for cancer. JAMA Oncology, 2(6), 762. https://doi.org/10.1001/jamaoncol.2015.6396.

[109]. Algra, A. M., & Rothwell, P. M. (2012). Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials. The Lancet Oncology, 13(5), 518–527. https://doi.org/10.1016/s1470-2045(12)70112-2.

[110]. Green, J., Czanner, G., Reeves, G., Watson, J., Wise, L., Roddam, A., &Beral, V. (2011). Menopausal hormone therapy and risk of gastrointestinal cancer: Nested case–control study within a prospective cohort, and meta- analysis. International Journal of Cancer, 130(10), 2387–2396. https://doi.org/10.1002/ijc.26236.

[111]. Brenner, H., Altenhofen, L., Stock, C., & Hoffmeister, M. (2013). Natural history of colorectal adenomas: birth cohort analysis among 3.6 million participants of screening colonoscopy. Cancer Epidemiology Biomarkers & Prevention, 22(6), 1043–1051. https://doi.org/10.1158/1055-9965.epi-13-0162.

[112]. Reddy, B. S. (2007). Strategies for colon cancer prevention. Sub-cellular Biochemistry/Subcellular Biochemistry, 213–225. https://doi.org/10.1007/1-4020-5688-5_10.

[113]. Walter, V., Jansen, L., Ulrich, A., Roth, W., Bläker, H., Chang-Claude, J., Hoffmeister, M., & Brenner, H. (2016). Alcohol consumption and survival of colorectal cancer patients: a population-based study from Germany ,. American Journal of Clinical Nutrition, 103(6), 1497–1506. https://doi.org/10.3945/ajcn.115.127092.

[114]. Ordóñez-Mena, J., Walter, V., Schöttker, B., Jenab, M., O'Doherty, M., Kee, F., Bueno-De-Mesquita, B., Peeters, P., Stricker, B., Ruiter, R., Hofman, A., Söderberg, S., Jousilahti, P., Kuulasmaa, K., Freedman, N., Wilsgaard, T., Wolk, A., Nilsson, L.,

Tjønneland, A., . . . Brenner, H. (2017). Impact of prediagnostic smoking and smoking cessation on colorectal cancer prognosis: a meta-analysis of individual patient data from cohorts within the CHANCES consortium. Annals of Oncology, 29(2), 472–483. https://doi.org/10.1093/annonc/mdx761.

[115]. Walter, V., Jansen, L., Hoffmeister, M., Ulrich, A., Chang-Claude, J., & Brenner, H. (2015). Smoking and survival of colorectal cancer patients: Population-based study from Germany. International Journal of Cancer, 137(6), 1433–1445. https://doi.org/10.1002/ijc.29511.

[116]. Walter, V., Jansen, L., Hoffmeister, M., & Brenner, H. (2014). Smoking and survival of colorectal cancer patients: systematic review and meta-analysis. Annals of Oncology, 25(8), 1517–1525. https://doi.org/10.1093/annonc/mdu040.

[117]. Dinicola, S., Morini, V., Coluccia, P., Proietti, S., D'Anselmi, F., Pasqualato, A., Masiello, M. G., Palombo, A., De Toma, G., Bizzarri, M., & Cucina, A. (2013). Nicotine increases survival in human colon cancer cells treated with chemotherapeutic drugs. Toxicology in Vitro, 27(8), 2256–2263. https://doi.org/10.1016/j.tiv.2013.09.020.

[118]. Sharma, A., Deeb, A., Iannuzzi, J. C., Rickles, A. S., Monson, J. R., & Fleming, F. J. (2012). Tobacco smoking and postoperative outcomes after colorectal surgery. Annals of Surgery, 258(2), 296–300. https://doi.org/10.1097/sla.0b013e3182708cc5.

[119]. Walter, V., Jansen, L., Knebel, P., Chang- Claude, J., Hoffmeister, M., & Brenner, H. (2017). Physical activity and survival of colorectal cancer patients: Population-based study from Germany. International Journal of Cancer, 140(9), 1985–1997. https://doi.org/10.1002/ijc.30619.

[120]. Otto, S. J., Korfage, I. J., Polinder, S., Van Der Heide, A., De Vries, E., Rietjens, J. a. C., &Soerjomataram, I. (2014). Association of change in physical activity and body weight with quality of life and mortality in colorectal cancer: a systematic review and meta-analysis. Supportive Care in Cancer, 23(5), 1237–1250. https://doi.org/10.1007/s00520-014-2480-0.

[121]. Van Blarigan, E. L., &Meyerhardt, J. A. (2015). Role of physical activity and diet after colorectal cancer diagnosis. Journal of Clinical Oncology, 33(16), 1825–1834. https://doi.org/10.1200/jco.2014.59.7799.

[122]. Friedenreich, C. M., Shaw, E., Neilson, H. K., & Brenner, D. R. (2017). Epidemiology and biology of physical activity and cancer recurrence. Journal of Molecular Medicine, 95(10), 1029–1041. https://doi.org/10.1007/s00109-017-1558-9.

[123]. Hong, J., & Park, J. (2021). Systematic Review: Recommendations of Levels of Physical Activity among Colorectal Cancer Patients (2010–2019). International Journal of Environmental Research and Public Health, 18(6), 2896. https://doi.org/10.3390/ijerph18062896.

[124]. Meyerhardt, J. A., Giovannucci, E. L., Holmes, M. D., Chan, A. T., Chan, J. A., Colditz, G. A., & Fuchs, C. S. (2006). Physical activity and survival after colorectal cancer diagnosis. Journal of Clinical Oncology, 24(22), 3527–3534. https://doi.org/10.1200/jco.2006.06.0855.

[125]. Guercio, B. J., Zhang, S., Ou, F., Venook, A. P., Niedzwiecki, D., Lenz, H., Innocenti, F., O'Neil, B. H., Shaw, J. E., Polite, B. N., Hochster, H. S., Atkins, J. N., Goldberg, R. M., Sato, K., Ng, K., Van Blarigan, E., Mayer, R. J., Blanke, C. D., O'Reilly, E. M., . . . Meyerhardt, J. A. (2019). Associations of physical activity with survival and progression in metastatic colorectal cancer: Results from cancer and leukemia Group B (Alliance)/SWOG 80405. Journal of Clinical Oncology, 37(29), 2620–2631. https://doi.org/10.1200/jco.19.01019.

[126]. Li, P., Wu, H., Zhang, H., Shi, Y., Xu, J., Ye, Y., Xia, D., Yang, J., Cai, J., & Wu, Y. (2014). Aspirin use after diagnosis but not prediagnosis improves established colorectal cancer survival: a meta-analysis. Gut, 64(9), 1419–1425. https://doi.org/10.1136/gutjnl-2014-308260.

[127]. Sostres, C., Gargallo, C. J., & Lanas, A. (2014). Aspirin, cyclooxygenase inhibition and colorectal cancer. World Journal of Gastrointestinal Pharmacology and Therapeutics, 5(1), 40. https://doi.org/10.4292/wjgpt.v5.i1.40.

[128]. Frouws, M. A., Van Herk-Sukel, M. P., Maas, H. A., Van De Velde, C. J., Portielje, J. E., Liefers, G., &Bastiaannet, E. (2017). The mortality reducing effect of aspirin in

colorectal cancer patients: Interpreting the evidence. Cancer Treatment Reviews, 55, 120–127. https://doi.org/10.1016/j.ctrv.2016.12.008.

[129]. Coyle, C., Cafferty, F., Vale, C., & Langley, R. (2016). Metformin as an adjuvant treatment for cancer: a systematic review and meta-analysis. Annals of Oncology, 27(12), 2184–2195. https://doi.org/10.1093/annonc/mdw410.

[130]. Weberpals, J., Jansen, L., Carr, P. R., Hoffmeister, M., & Brenner, H. (2016). Beta blockers and cancer prognosis – The role of immortal time bias: A systematic review and meta-analysis. Cancer Treatment Reviews, 47, 1–11. https://doi.org/10.1016/j.ctrv.2016.04.004.

[131]. Maalmi, H., Walter, V., Jansen, L., Chang-Claude, J., Owen, R. W., Ulrich, A., Schöttker, B., Hoffmeister, M., & Brenner, H. (2017). Relationship of very low serum 25-hydroxyvitamin D3 levels with long-term survival in a large cohort of colorectal cancer patients from Germany. European Journal of Epidemiology, 32(11), 961–971. https://doi.org/10.1007/s10654-017-0298-z.

[132]. Zgaga, L., Theodoratou, E., Farrington, S. M., Din, F. V., Ooi, L. Y., Glodzik, D., Johnston, S., Tenesa, A., Campbell, H., & Dunlop, M. G. (2014). Plasma vitamin D concentration influences survival outcome after a diagnosis of colorectal cancer. Journal of Clinical Oncology, 32(23), 2430–2439. https://doi.org/10.1200/jco.2013.54.5947.

[133]. Vaughan-Shaw, P. G., Buijs, L. F., Blackmur, J. P., Theodoratou, E., Zgaga, L., Din, F. V. N., Farrington, S. M., & Dunlop, M. G. (2020). The effect of vitamin D supplementation on survival in patients with colorectal cancer: systematic review and meta-analysis of randomised controlled trials. British Journal of Cancer, 123(11), 1705–1712. https://doi.org/10.1038/s41416-020-01060-8.

[134]. Boughanem, H., Canudas, S., Hernandez-Alonso, P., Becerra-Tomás, N., Babio, N., Salas-Salvadó, J., & Macias-Gonzalez, M. (2021). Vitamin D intake and the risk of colorectal Cancer: An Updated Meta-Analysis and Systematic Review of Case-Control and Prospective Cohort Studies. Cancers, 13(11), 2814. https://doi.org/10.3390/cancers13112814.

[135]. Ng, K., Nimeiri, H. S., McCleary, N. J., Abrams, T. A., Yurgelun, M. B., Cleary, J. M., Rubinson, D. A., Schrag, D., Allen, J. N., Zuckerman, D. S., Miksad, R. A., Chan, E., Constantine, M., Weckstein, D., Faggen, M. G., Thomas, C. A., Kournioti, C. S., Mackintosh, C., Zheng, H., & Fuchs, C. S. (2017). SUNSHINE: Randomized double-blind phase II trial of vitamin D supplementation in patients with previously untreated metastatic colorectal cancer. Journal of Clinical Oncology, 35(15_suppl), 3506. https://doi.org/10.1200/jco.2017.35.15_suppl.3506.

[136]. Brenner, H., Jansen, L., Saum, K., Holleczek, B., &Schöttker, B. (2017). Vitamin D Supplementation Trials Aimed at Reducing Mortality Have Much Higher Power When Focusing on People with Low Serum 25-Hydroxyvitamin D Concentrations. Journal of Nutrition, 147(7), 1325–1333. https://doi.org/10.3945/jn.117.250191.

[137]. Dawson, H., Kirsch, R., Messenger, D., &Driman, D. (2019). A review of current challenges in colorectal cancer reporting. Archives of Pathology &Laboratory Medicine, 143(7), 869–882. https://doi.org/10.5858/arpa.2017-0475-ra

[138]. N, M. K., Pc, S., & Prabhu, G. (2019). Domain-Based analysis of colon polyp in CT colonography using Image-Processing techniques. Asian Pacific Journal of Cancer Prevention, 20(2), 629–637. https://doi.org/10.31557/apjcp.2019.20.2.629.

[139]. Grimm, I. S., & McGill, S. K. (2019). Look, but don't touch: what not to do in managing large colorectal polyps. Gastrointestinal Endoscopy, 89(3), 479–481. https://doi.org/10.1016/j.gie.2018.10.008.

[140]. Messersmith, W. A. (2019). NCCN Guidelines Updates: Management of Metastatic Colorectal Cancer. PubMed, 17(5.5), 599–601. https://doi.org/10.6004/jnccn.2019.5014.

[141]. Xie, Y., Chen, Y., & Fang, J. (2020). Comprehensive review of targeted therapy for colorectal cancer. Signal Transduction and Targeted Therapy, 5(1). https://doi.org/10.1038/s41392-020-0116-z.

[142]. Sadreddini, S., Safaralizadeh, R., Baradaran, B., Aghebati-Maleki, L., Hosseinpour-Feizi, M. A., Shanehbandi, D., Jadidi-Niaragh, F., Sadreddini, S., Kafil, H. S., Younesi, V., & Yousefi, M. (2016). Chitosan nanoparticles as a dual drug/siRNA delivery system for treatment of colorectal cancer. Immunology Letters, 181, 79–86. https://doi.org/10.1016/j.imlet.2016.11.013.

[143]. Armaghany T, Wilson JD, Chu Q, Mills G. Genetic alterations in colorectal cancer. Gastrointest Cancer Res. 2012 Jan;5(1):19-27. PMID: 22574233; PMCID: PMC3348713.

[144]. Ginn, S. L., Amaya, A. K., Alexander, I. E., Edelstein, M., & Abedi, M. R. (2018). Gene therapy clinical trials worldwide to 2017: An update. The Journal of Gene Medicine, 20(5). https://doi.org/10.1002/jgm.3015.

[145]. Durai R, Yang SY, Seifalian AM, Winslet MC. Principles and applications of gene therapy in colon cancer. J Gastrointestin Liver Dis. 2008 Mar;17(1):59-67. PMID: 18392246.

[146]. Zhang, J., Kale, V., & Chen, M. (2014). Gene-Directed Enzyme Prodrug Therapy. The AAPS Journal, 17(1), 102–110. https://doi.org/10.1208/s12248-014-9675-7.

[147]. Zahavi, D., & Weiner, L. (2020). Monoclonal antibodies in cancer therapy. Antibodies, 9(3), 34. https://doi.org/10.3390/antib9030034.

[148]. Saleh, K., Khalife-Saleh, N., Kourie, H. R., & Chahine, G. (2017). How and when adjuvant treatment should be intensified in stage III colorectal cancers? Future Oncology, 13(22), 1999–2006. https://doi.org/10.2217/fon-2017-0197.

[149]. Cunningham, D., Humblet, Y., Siena, S., Khayat, D., Bleiberg, H., Santoro, A., Bets, D., Mueser, M., Harstrick, A., Verslype, C., Chau, I., & Van Cutsem, E. (2004). Cetuximab Monotherapy and Cetuximab plus Irinotecan in Irinotecan-Refractory Metastatic Colorectal Cancer. New England Journal of Medicine, 351(4), 337–345. https://doi.org/10.1056/nejmoa033025.

[150]. Sharma, P., & Allison, J. P. (2015). Immune Checkpoint Targeting in Cancer Therapy: Toward Combination Strategies with Curative Potential. Cell, 161(2), 205–214. https://doi.org/10.1016/j.cell.2015.03.030

[151]. Hu, Z., Ott, P. A., & Wu, C. J. (2017). Towards personalized, tumour-specific, therapeutic vaccines for cancer. Nature Reviews. Immunology, 18(3), 168–182. https://doi.org/10.1038/nri.2017.131

[152]. Lesterhuis, W., De Vries, I., Schuurhuis, D., Boullart, A., Jacobs, J., De Boer, A., Scharenborg, N., Brouwer, H., Van De Rakt, M., Figdor, C., Ruers, T., Adema, G., & Punt, C. (2006). Vaccination of colorectal cancer patients with CEA-loaded dendritic cells: antigen-specific T cell responses in DTH skin tests. Annals of Oncology, 17(6), 974–980. https://doi.org/10.1093/annonc/mdl072

[153]. Fong, L., Hou, Y., Rivas, A., Benike, C., Yuen, A., Fisher, G. A., Davis, M. M., & Engleman, E. G. (2001). Altered peptide ligand vaccination with Flt3 ligand expanded dendritic cells for tumor immunotherapy. Proceedings of the National Academy of Sciences, 98(15), 8809–8814. https://doi.org/10.1073/pnas.141226398

[154]. Orsini, G., Legitimo, A., Failli, A., Ferrari, P., Nicolini, A., Spisni, R., Miccoli, P., & Consolini, R. (2013). Defective Generation and Maturation of Dendritic Cells from Monocytes in Colorectal Cancer Patients during the Course of Disease. International Journal of Molecular Sciences, 14(11), 22022–22041. https://doi.org/10.3390/ijms141122022

[155]. Wu, D., Wu, P., Wu, X., Ye, J., Wang, Z., Zhao, S., Ni, C., Hu, G., Xu, J., Han, Y., Zhang, T., Qiu, F., Yan, J., & Huang, J. (2015). Ex vivoexpanded human circulating Vδ1 γδT cells exhibit favorable therapeutic potential for colon cancer. OncoImmunology, 4(3), e992749. https://doi.org/10.4161/2162402x.2014.992749

[156]. Downs-Canner, S., Magge, D., Ravindranathan, R., O'Malley, M. E., Francis, L., Liu, Z., Guo, Z. S., Obermajer, N., & Bartlett, D. L. (2015). Complement inhibition: a novel form of immunotherapy for colon cancer. Annals of Surgical Oncology, 23(2), 655–662. https://doi.org/10.1245/s10434-015-4778-7

[157]. West, N. R., McCuaig, S., Franchini, F., & Powrie, F. (2015). Emerging cytokine networks in colorectal cancer. Nature Reviews. Immunology, 15(10), 615–629. https://doi.org/10.1038/nri3896

[158]. Hossain, M. S., & Urbi, Z. (2016). Effect of Naphthalene Acetic Acid on the Adventitious Rooting in Shoot Cuttings

ofAndrographispaniculata(Burm.f.) Wall. ex Nees: An Important Therapeutical Herb. International Journal of Agronomy, 2016, 1–6. https://doi.org/10.1155/2016/1617543.

[159]. Hossain, M. S., Urbi, Z., Sule, A., & Rahman, K. M. H. (2014). Andrographis paniculata(Burm. f.) Wall. ex Nees: A Review of Ethnobotany, Phytochemistry, and Pharmacology. The Scientific World JOURNAL, 2014, 1–28. https://doi.org/10.1155/2014/274905.

[160]. Farooq, U., Khan, T., Shah, S. A., Hossain, M. S., Ali, Y., Ullah, R., Raziq, N., Shahid, M., & Capasso, R. (2021). Isolation, characterization and neuroprotective activity of folecitin: an in vivo study. Life, 11(8), 825. https://doi.org/10.3390/life11080825

[161]. Urbi Z., Hossain M.S., Rahman K.M.H., Zayed T.M. Grape: A medicinal fruit species in the holy Qur'an and its ethnomedicinal importance. World Appl. Sci. J. 2014;30:253–265.

[162]. Newman, D. J., & Cragg, G. M. (2016). Natural Products as Sources of New Drugs from 1981 to 2014. Journal of Natural Products, 79(3), 629–661. https://doi.org/10.1021/acs.jnatprod.5b01055

[163]. Huang, X., Yang, Z., Xie, Q., Zhang, Z., Zhang, H., & Ma, J. (2019). Natural products for treating colorectal cancer: A mechanistic review. Biomedicine & Pharmacotherapy, 117, 109142. https://doi.org/10.1016/j.biopha.2019.109142

[164]. Shi, M., Lin, H., Lee, Y., Chao, J., Lin, R., & Chen, J. (2008). Inhibition of cell-cycle progression in human colorectal carcinoma Lovo cells by andrographolide. Chemico-Biological Interactions, 174(3), 201–210. https://doi.org/10.1016/j.cbi.2008.06.006

[165]. Ge, L., Wang, Y., Tian, J., Mao, L., Zhang, J., Zhang, J., Shen, X., & Yang, K. (2016). Network meta-analysis of Chinese herb injections combined with FOLFOX chemotherapy in the treatment of advanced colorectal cancer. Journal of Clinical Pharmacy and Therapeutics, 41(4), 383–391. https://doi.org/10.1111/jcpt.12410

[166]. O'Keefe, S. J. (2019). The association between dietary fibre deficiency and high-income lifestyle-associated diseases: Burkitt's hypothesis revisited. ˜ the œLancet. Gastroenterology & Hepatology, 4(12), 984–996. https://doi.org/10.1016/s2468-1253(19)30257-2

[167]. Coussens, L. M., & Werb, Z. (2002). Inflammation and cancer. Nature, 420(6917), 860–867. https://doi.org/10.1038/nature01322