
بسم الله الرحمن الرحيم

Genes involved in familial colorectal cancer

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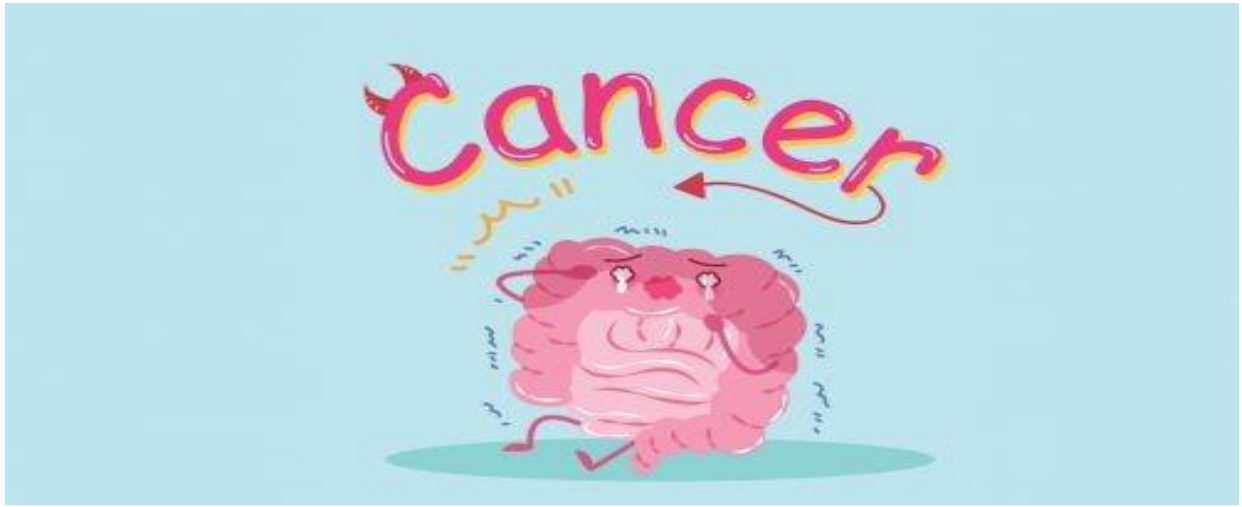


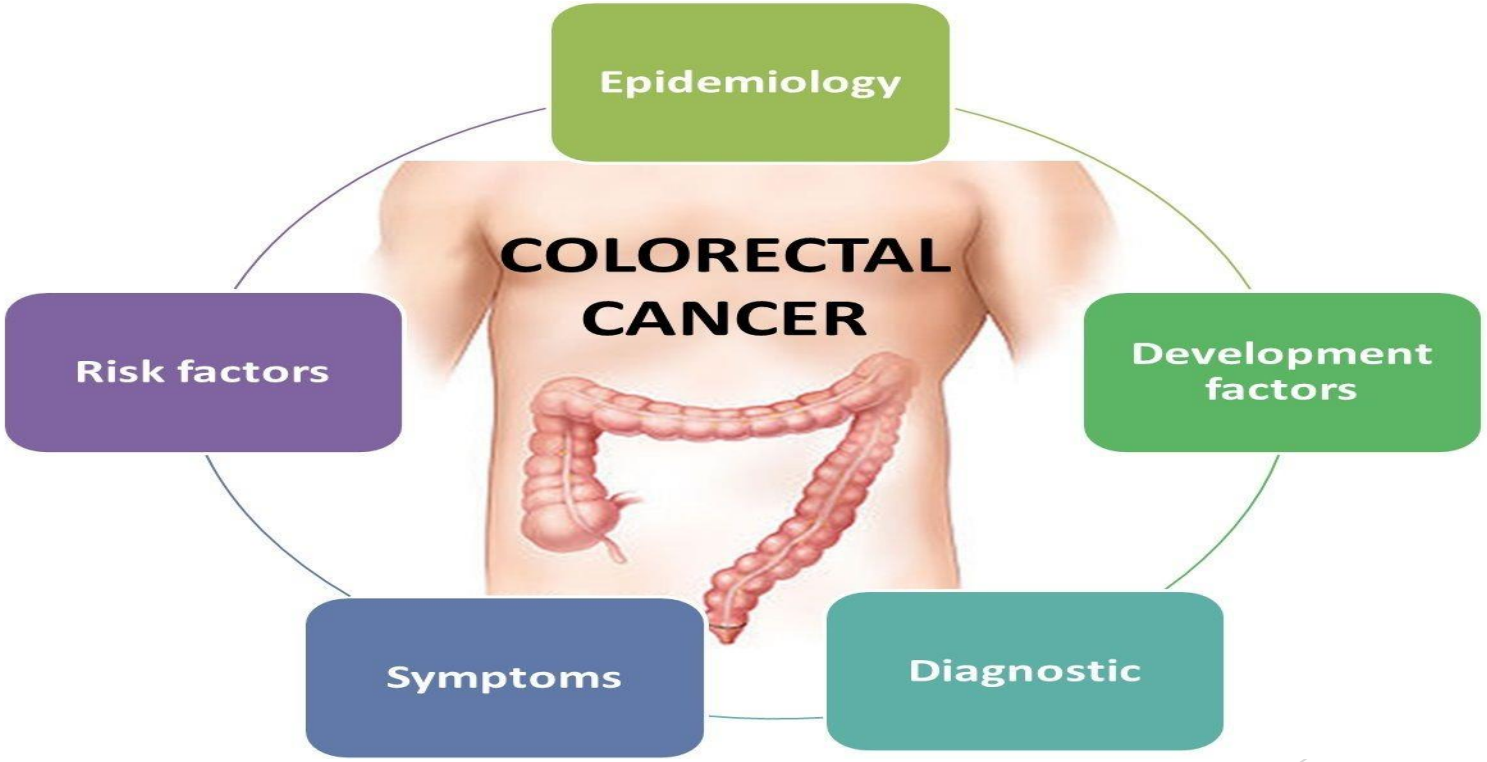
Introduction

Cancer is a genetic disease, and the number and type of altered genes that produce its phenotype, including proliferation, motility, and drug resistance, are high, heterogeneous, and largely unknown.

When studying metastatic patients, we focus on a specific situation and moment in the genetic evolution of the cancer, and eliminate consecutive events that have accumulated and progressed in time and space from a normal cell to a neoplastic cell. In fact, it is quite impossible to trace this genetic "cascade" in a patient, because when it is clinically known, the tumor mass has already gone through a large part of its genetic history.

Thus, existing studies compare normal cells, early, middle, or advanced cancers of different groups of patients.

These strong and uncontrollable biases are associated with physiological genetic polymorphisms (race, age, sex) and the presence of other comorbidities that often have genetic mediators in common with cancer(diabetes, hypertension ,obesity).

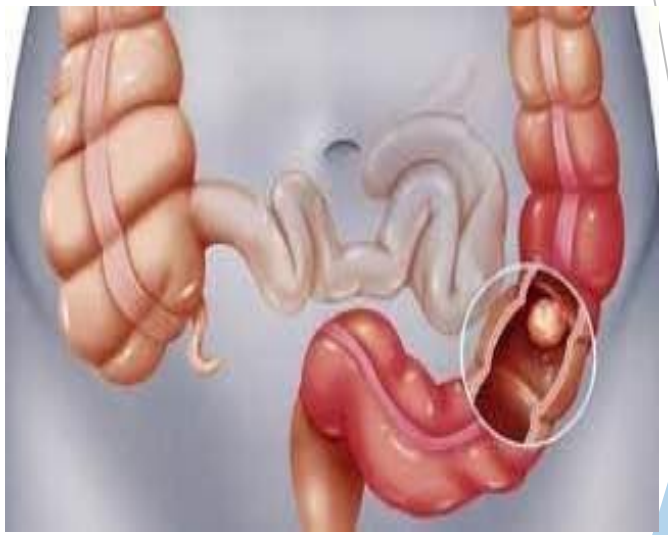


Introduction

Recent studies with primary and metastatic tumors removed surgically, if any, at different times in a patient's clinical history, at different times in the clinical history, have recently developed a strategy to include this the problem is used.

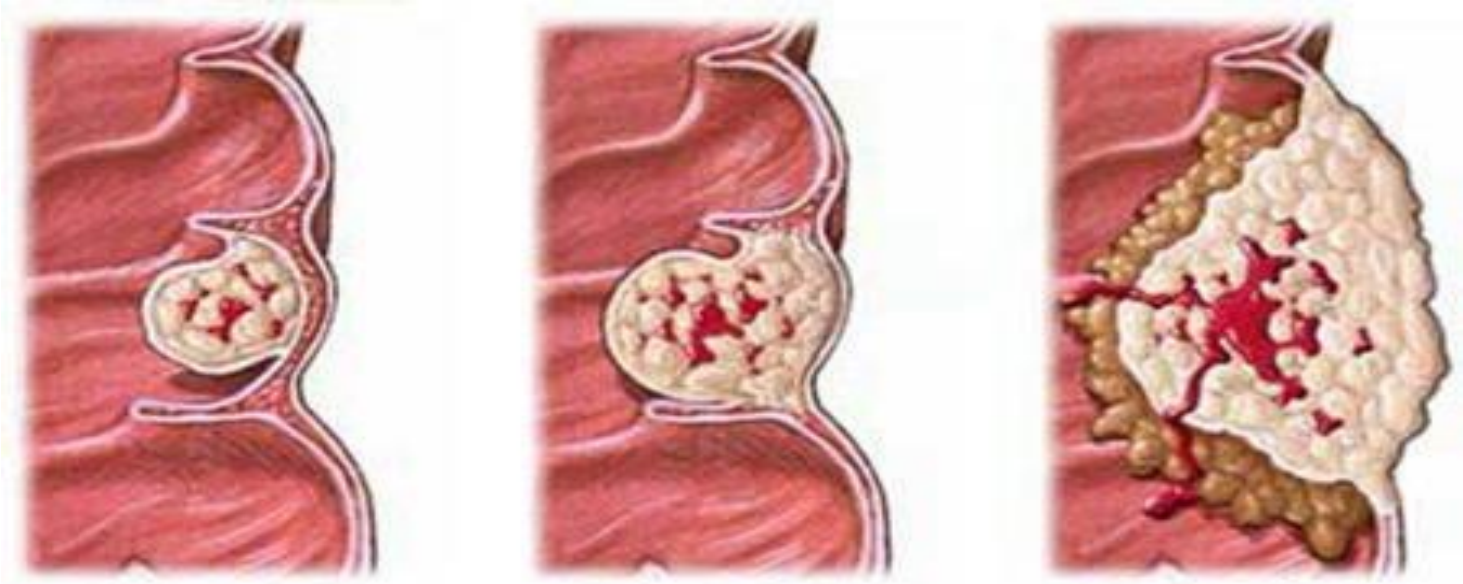
Colorectal cancer (CRC) is caused by multiple genetic changes. Some of the genes involved have been extensively studied (APC, TP53, KRAS, SMAD4, PIK3CA, MMR genes) in highly heterogeneous and multi-metastatic groups.

However, about 10% of metastatic CRC patients present with a passive oligo-metastatic disease different from other patients with a Multi-static and invasive clinical course.

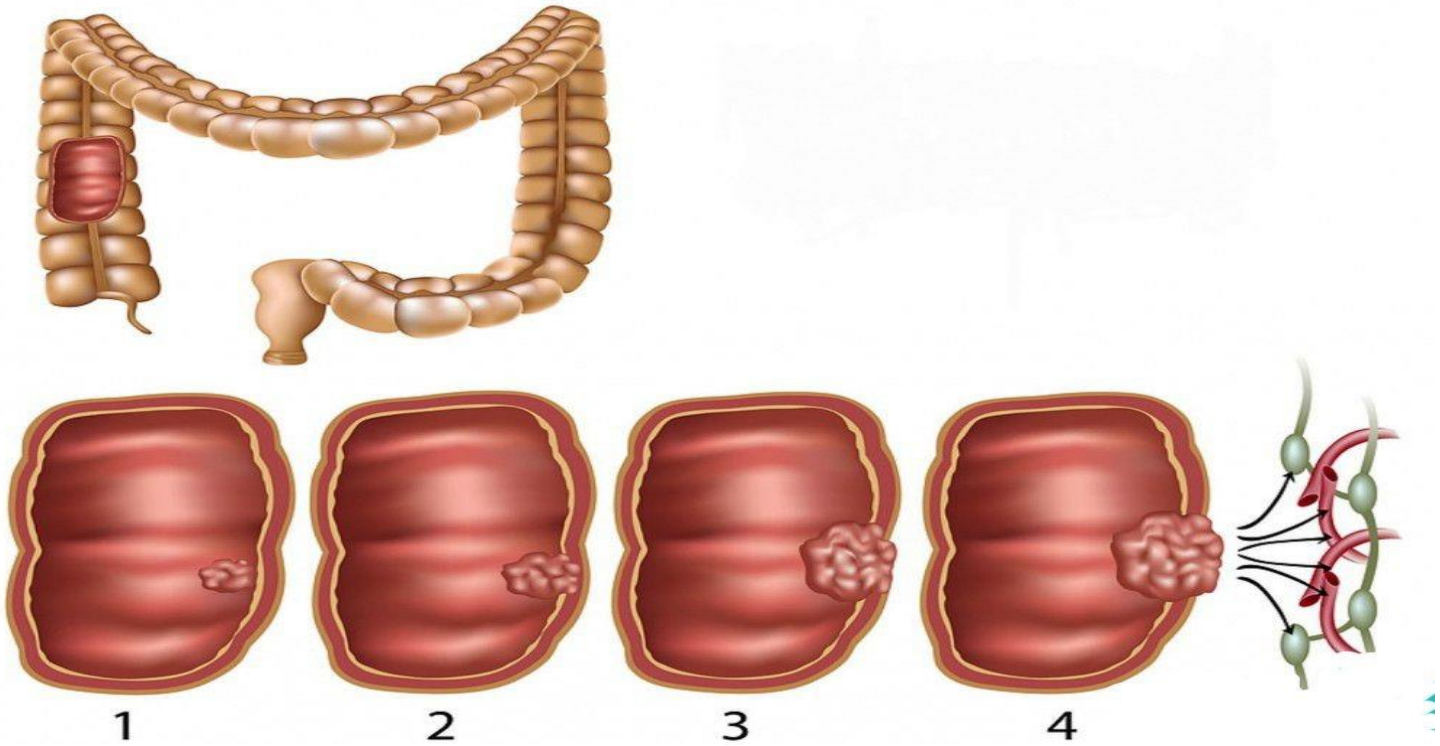


Genetic dynamics difference between oligo CRC and poly mastic:
Understanding the genetic (primary → metastatic) pathways of CRC is crucial in patients selected to demonstrate homogeneous clinical models, to establish genotype / phenotype correlations, and to identify molecular events that lead to an increasing malignant phenotype.

This information is essential for planning innovative treatment strategies aimed at reversing or controlling these phenomena

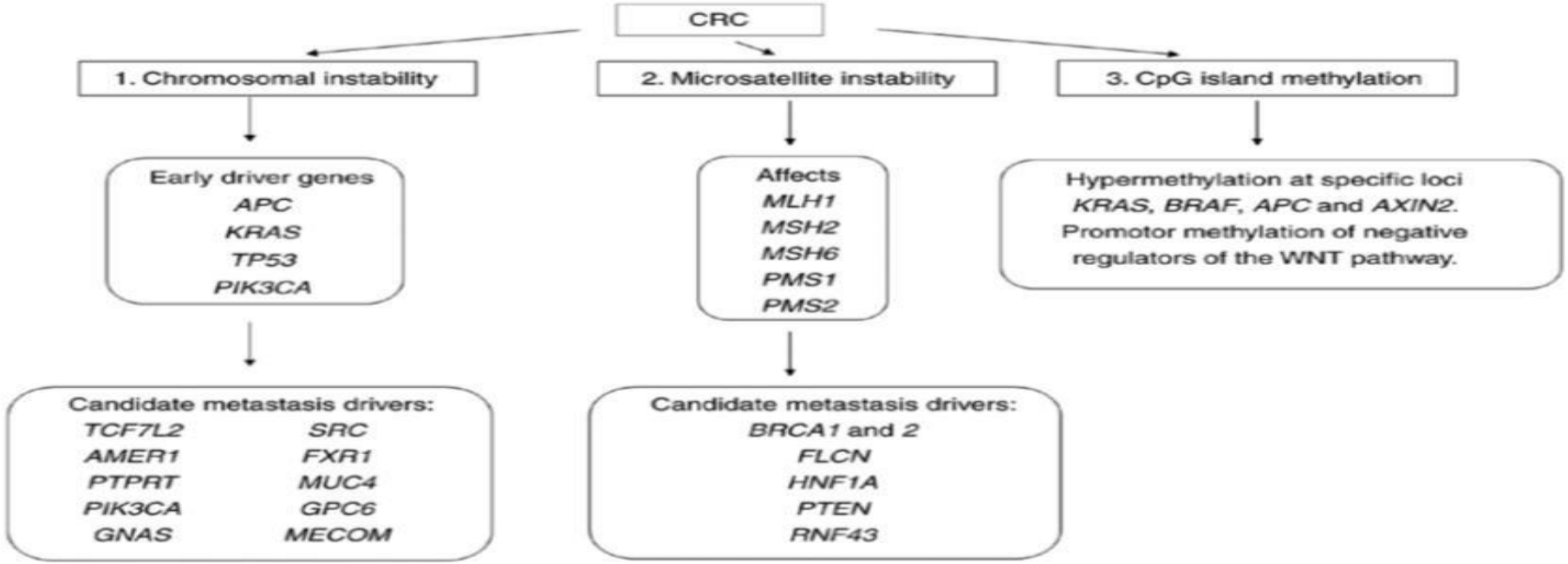


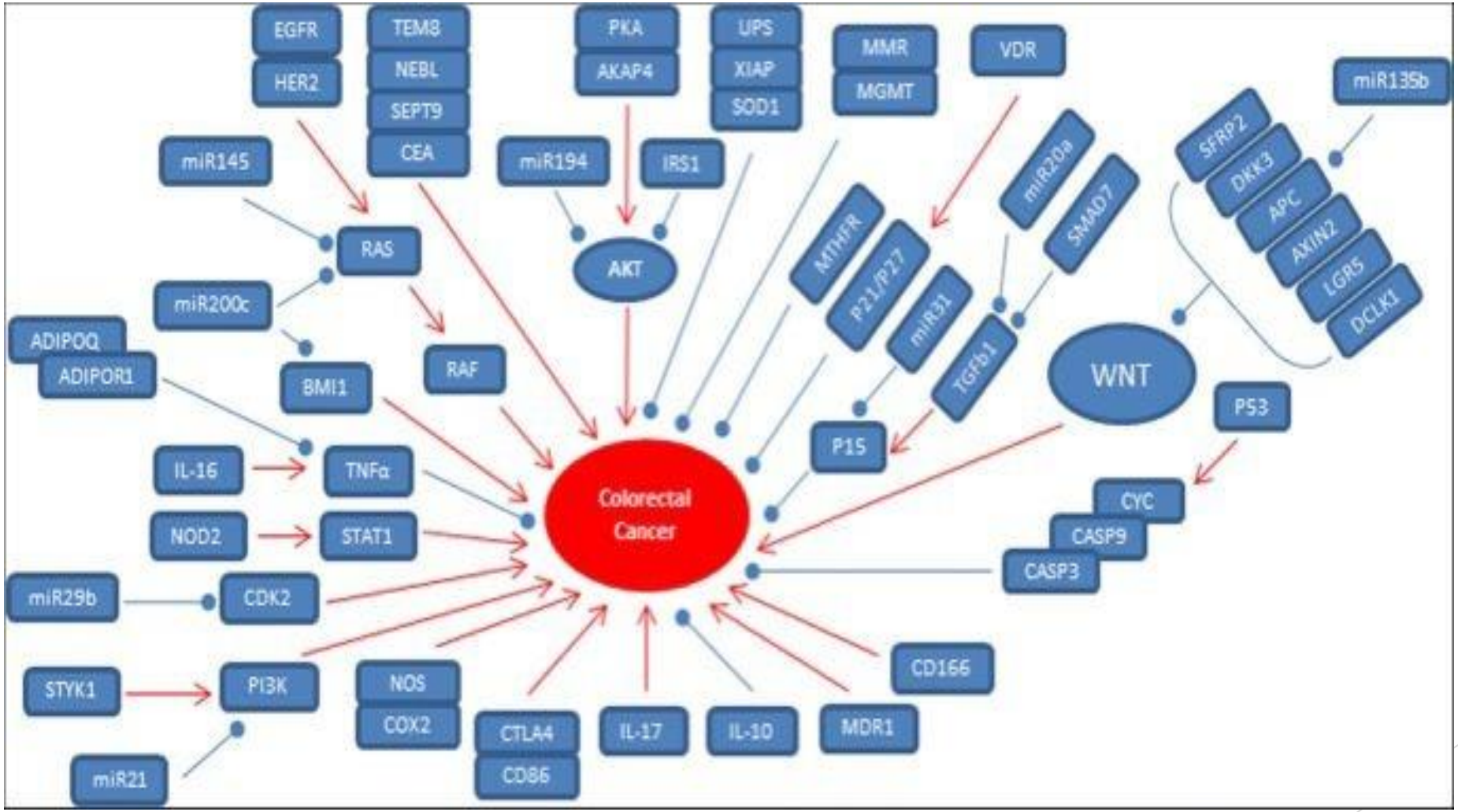
Understanding the genetic evolution of colorectal cancer (CRC) is essential to identifying the molecular events that lead the disease to an increasingly malignant phenotype, and therefore, planning treatment strategies aimed at reversing or controlling these phenomena.



Genotype-phenotype correlation in CRC:

Comorbidities and cancer heterogeneity Genetic progression from natural mucosa to adenocarcinoma relies on the sequential accumulation of several gene, which begin with "cancer fields" caused by inherited mutations, natural DNA replication errors, or mutagenic insults .
Some of them are critical for the acquisition of malignant phenotypes (key stimulus genes) and are often found in cancer cells.




EGFR
HER2
TEM8
NEBL
SEPT9
CEA
PKA
AKAP4
UPS
XIAP
SOD1
MMR
MGMT
VDR
miR135b
miR145
miR194
IRS1
miR20a
SMAD7
SFRP2
DKK3
APC
AXIN2
LGR5
DCLK1
MTHFR
P21/P27
miR31
TGFb1
RAS
AKT
miR200c
ADIPOQ
ADIPOR1
BMI1
RAF
WNT
P53
P15
IL-16
TNFα
NOD2
STAT1
Colorectal Cancer
CYC
CASP9
CASP3
miR29b
CDK2
STYK1
PI3K
NOS
COX2
CTLA4
CD86
IL-17
IL-10
MDR1
CD166
miR21

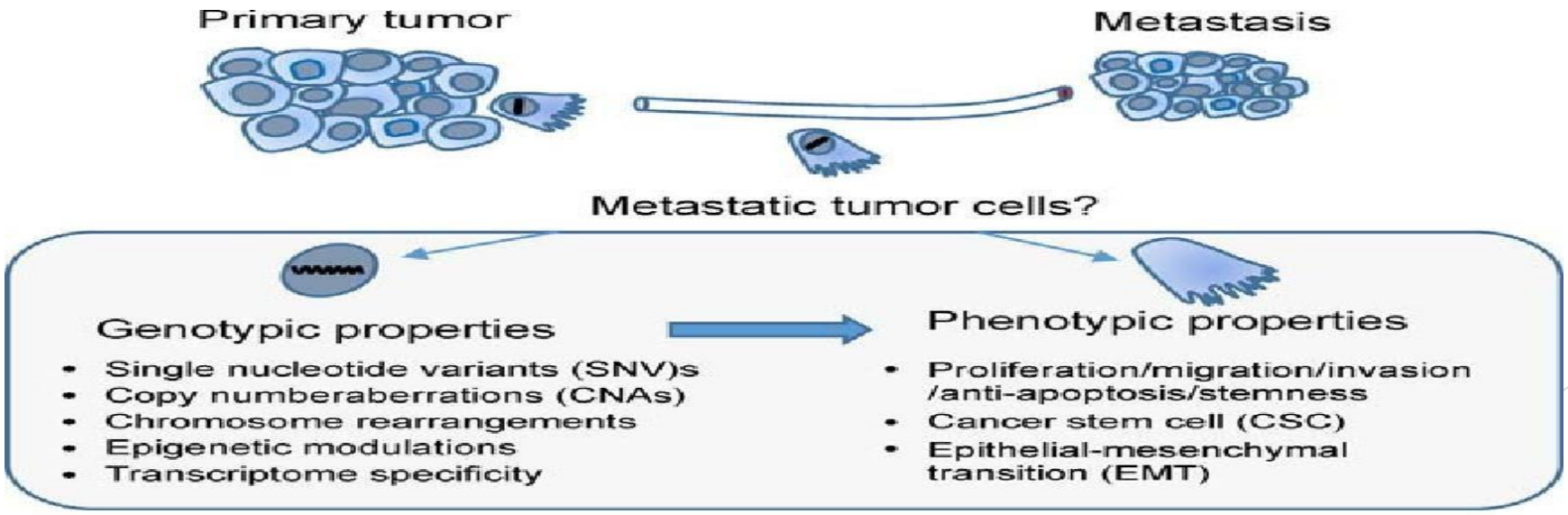
	CRC≤50	%	CRC>50	%	OR	lower	upper	*P*-value
Age								
AA/AA	97	5	1,841	95	1.000			1.000
AA/GC	2	3.8	50	96.2	1.317	0.316	5.493	
Total	99		1,891					
	Female	%	Male	%	OR	lower	upper	*P*-value
Gender								
AA/AA	766	39.5	1,172	60.5	1.000			0.388
AA/GC	17	32.7	35	67.3	1.346	0.749	2.419	
Total	783		1,207					
	Colon	%	Rectum	%	OR	lower	upper	*P*-value
CRC location								
AA/AA	1,267	65.9	656	34.1	1.000			0.882
AA/GC	33	64.7	18	35.3	1.053	0.589	1.885	
Total	1,300		674					
	No	%	Yes	%	OR	lower	upper	*P*-value
Previous neoplasm								
AA/AA	1,290	73.8	458	26.2	1.000			0.624
AA/GC	39	78	11	22	0.794	0.403	1.564	
Total	1,329		469					
	No	%	Yes	%	OR	lower	upper	*P*-value
Prev/sync adenoma								
AA/AA	1,268	71.2	513	28.8	1.000			0.112
AA/GC	41	82	9	18	0.543	0.262	1.124	
Total	1,309		522					
	No	%	Yes	%	OR	lower	upper	*P*-value
CRC FH								
AA/AA	1,652	85.2	286	14.8	1.000			0.026
AA/GC	50	96.2	2	3.8	0.231	0.056	0.955	
Total	1,702		288					
	No	%	Yes	%	OR	lower	upper	*P*-value
Lynch FH								
AA/AA	1,401	81.5	317	18.5	1.000			0.048
AA/GC	42	93.3	3	6.7	0.316	0.097	1.025	
Total	1,443		320					
	No	%	Yes	%	OR	lower	upper	*P*-value
MSI								
AA/AA	1,308	94	84	6	1.000			0.731
AA/GC	37	92.5	3	7.5	1.263	0.381	4.180	
Total	1,345		87					
	I–II	%	III–IV	%	OR	lower	upper	*P*-value
TNM								
AA/AA	909	53.7	783	46.3	1.000			1.000
AA/GC	26	53.1	23	46.9	1.027	0.581	1.814	
Total	935		806					

CRC, colorectal cancer; OR, odds ratio; Prev/Sync, Previous/Synchronous; FH, family history; MSI, microsatellite instability; TNM, tumor-node-metastasis.
doi:10.1371/journal.pone.0095022.t002

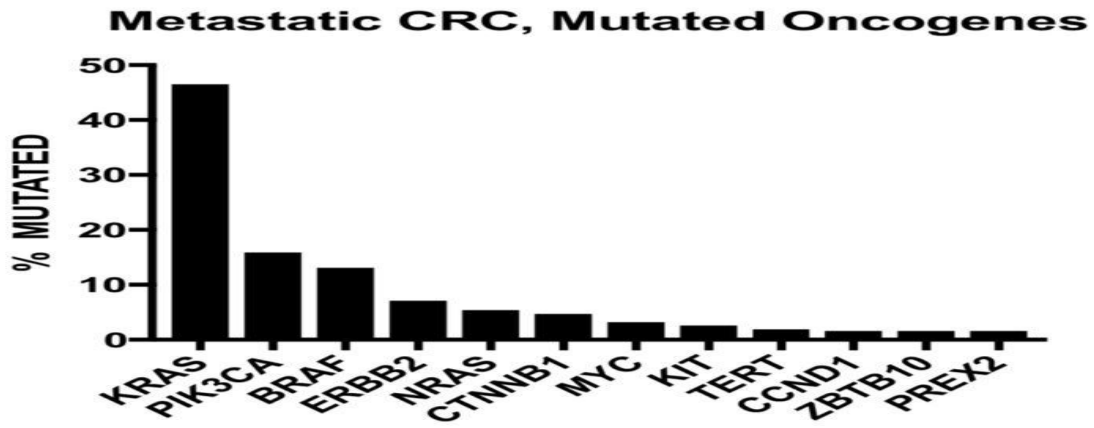
Metastatic CRCs are among the tumors displaying the highest levels of single-nucleotide variants (SNVs), with only urinary tract, esophagus, lung cancers and melanoma exhibiting higher levels among 20 different types of metastatic cancers.

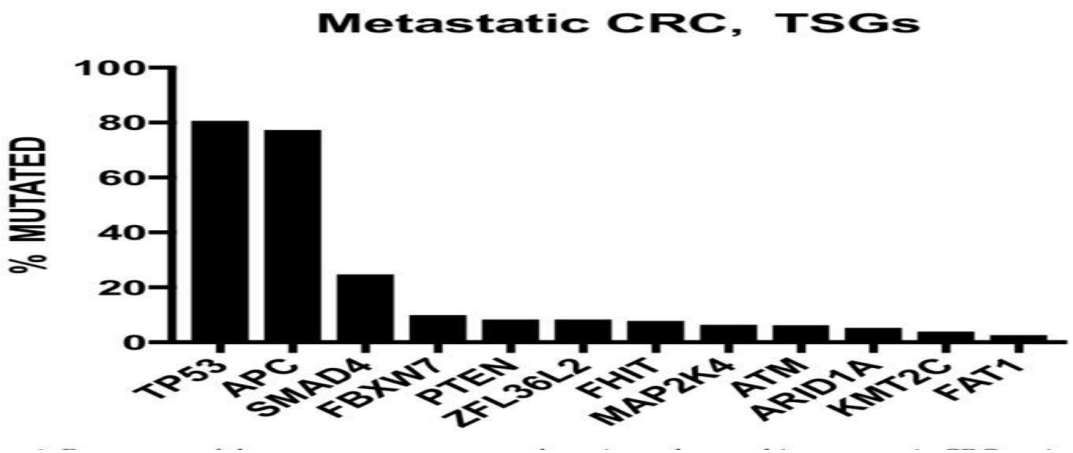
Only 4% of metastatic CRCs displayed an MSI genotype/phenotype, a frequency that is lower than that reported for primary CRC, a finding that can be explained by the lower tendency of these tumors to metastasize.

Copy number alterations are frequent in metastatic CRC; an extreme form of CNA can be caused by whole genome duplication (WGD), an event frequent (>60% of cases) in metastatic CRCs, among the metastatic tumors most frequently showing WGD.

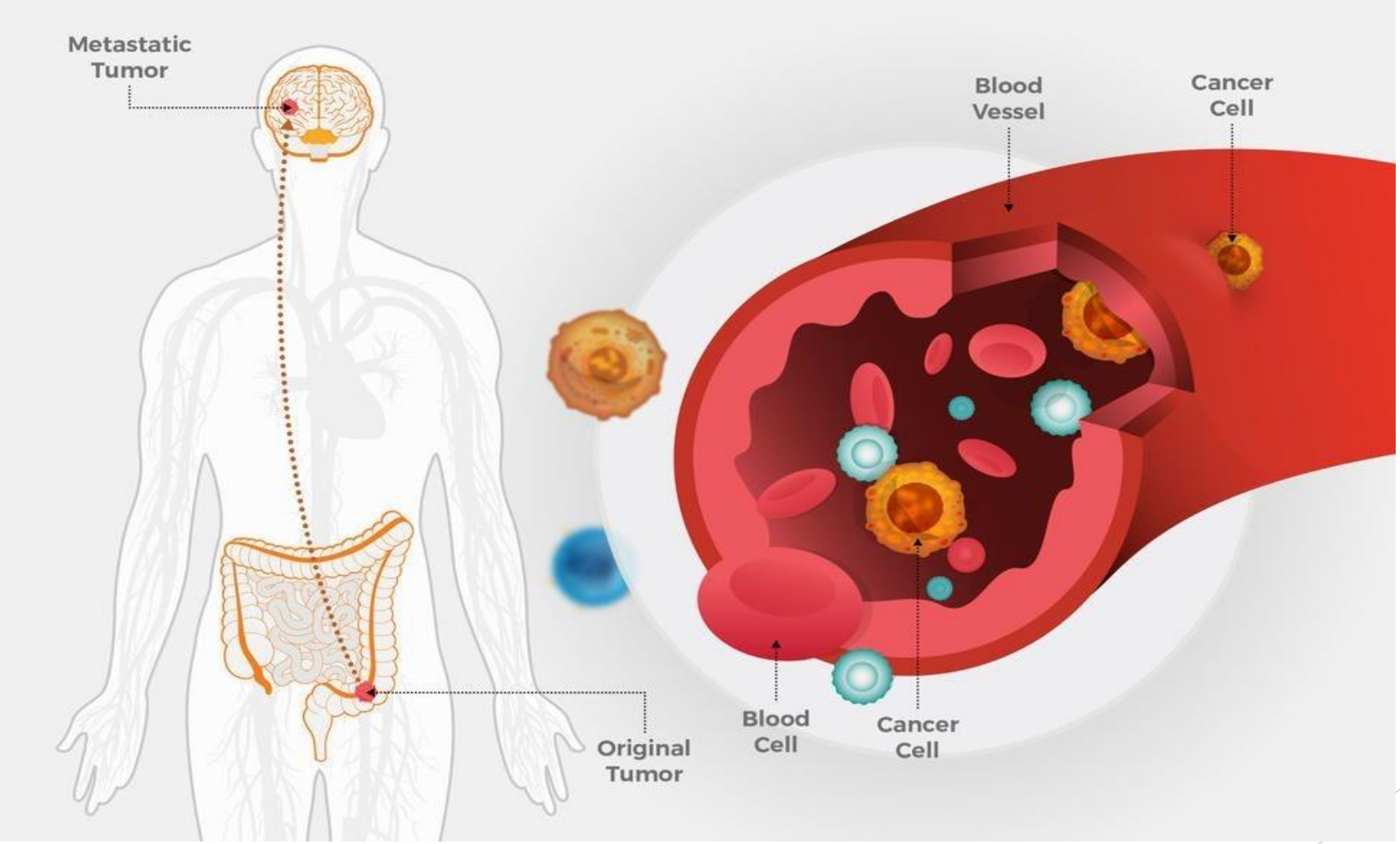


Frequency of the most recurrent gene alterations observed in metastatic CRC patients .
Were based on the wide-genome sequencing analysis of 372 metastatic CRC patients.





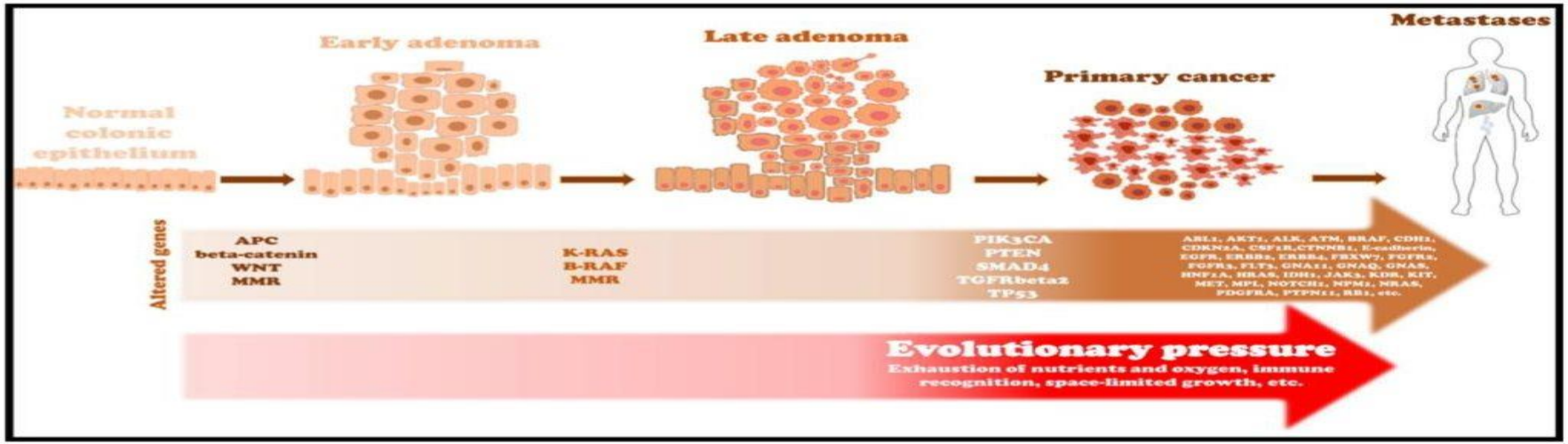
Colorectal cancer cells can break away from the original tumor and travel through the blood or lymph system to other parts of the body, including the liver, lungs, and brain.

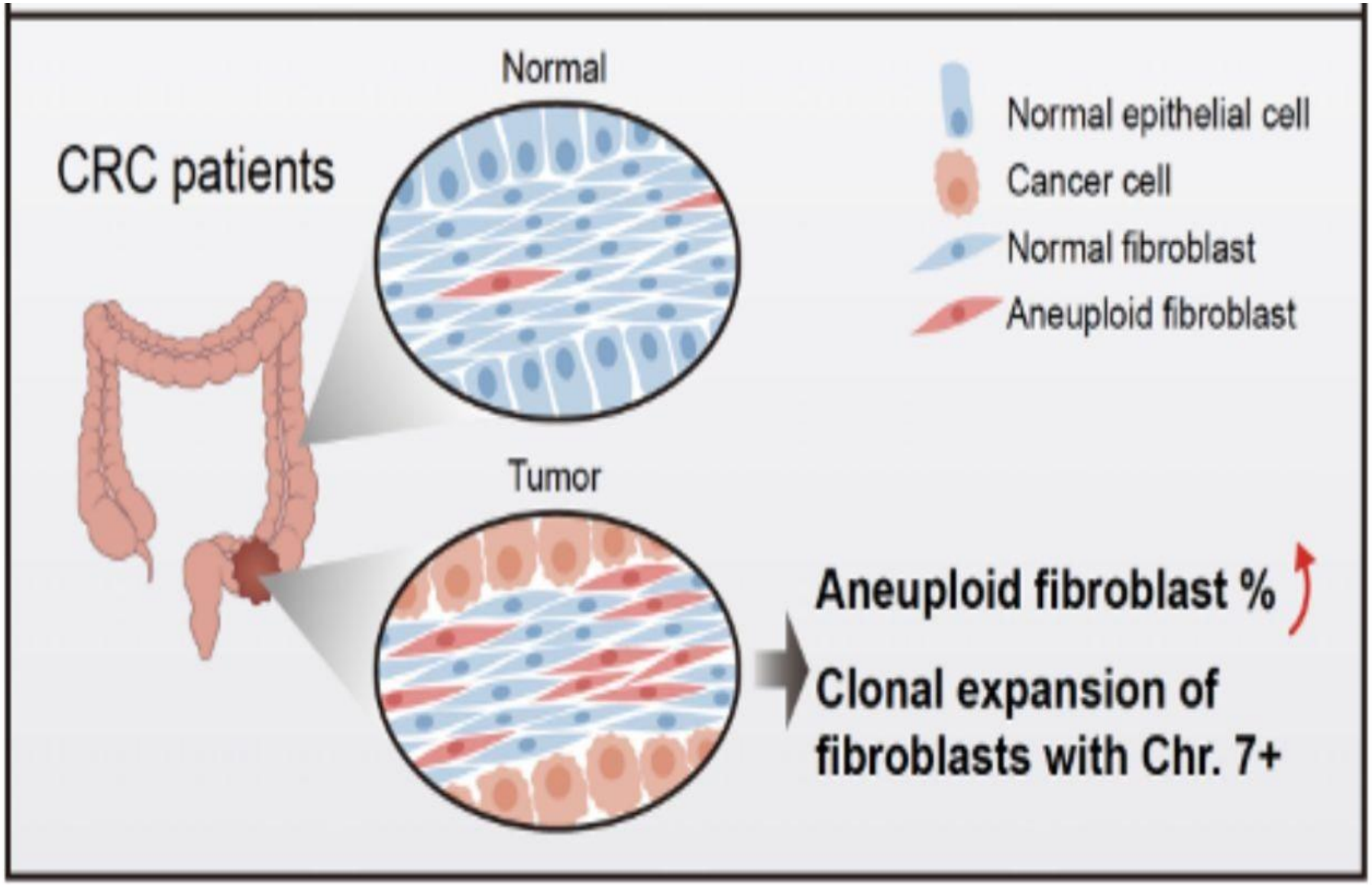


Progressive accumulation of specific genetic alterations and environmental factors push the evolution from adenocarcinoma precursors to malignant lesions.

Studies on correlations between genotype and phenotype in cancer are extremely difficult.
In fact, except for very rare cases including some inherited forms of tumors (retinoblastoma, Wilms' tumor, etc.), cancer arises as an acquired multi-genic disease.

The first and most important limit on a methodologic point of view to make genotype/phenotype correlations is represented by the selection of "clean" human models of cancer- In fact, several genes involved in highly common diseases strongly contribute to cancer heterogeneity, i.e. hypertension , diabetes , allergies and inflammatory chronic diseases.

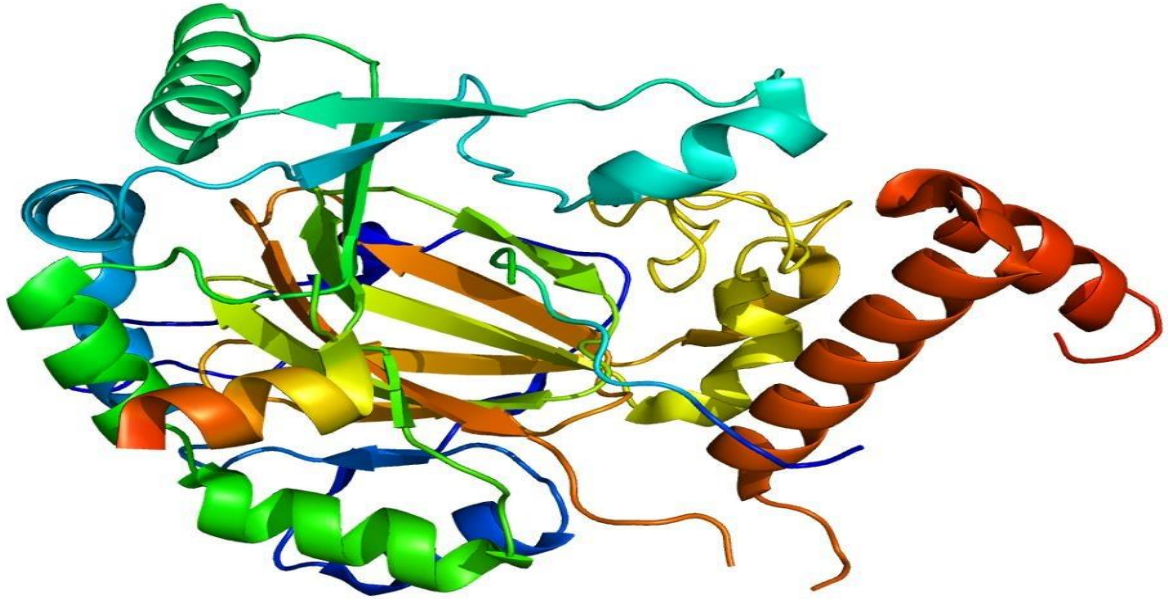



Normal
CRC patients
Normal epithelial cell
Cancer cell
Normal fibroblast
Aneuploid fibroblast
Tumor
Aneuploid fibroblast %
Clonal expansion of
fibroblasts with Chr. 7+

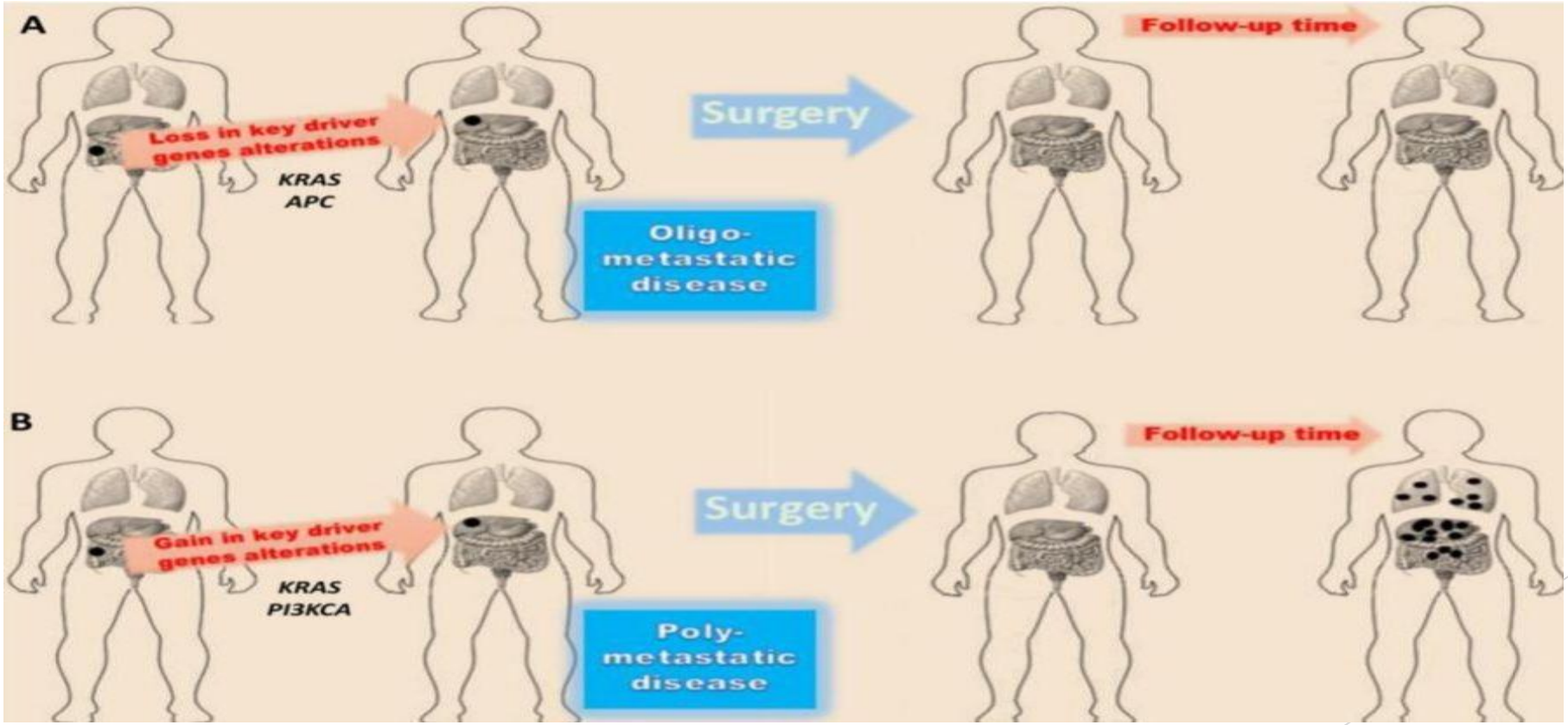
These diseases interfere with cancer genetics; in fact, some genes in evolved in cancer-related phenomena (as proliferation and angiogenesis) are altered in hypertension and atherosclerotic plaque or they are induced as a consequence of hypoxia, oxidative stress.

HIF-1 (Hypoxia-Inducible Factor-1) and LOX-1 (Lectin-like Oxidized low-density lipoprotein receptor-1) genes products are the most important mediator between chronic cardio-vascular diseases and cancer .

HIF-1 induces the expression of multiple tumor angiogenic factors including VEGF (Vascular Endothelial Growth Factor) and other growth factors . Furthermore, HIF-1 is also involved in promoting the oxidative stress through reactive oxygen species (ROS) and inflammatory pathways through nuclear factor-kappa B activation in atherosclerotic plaques .

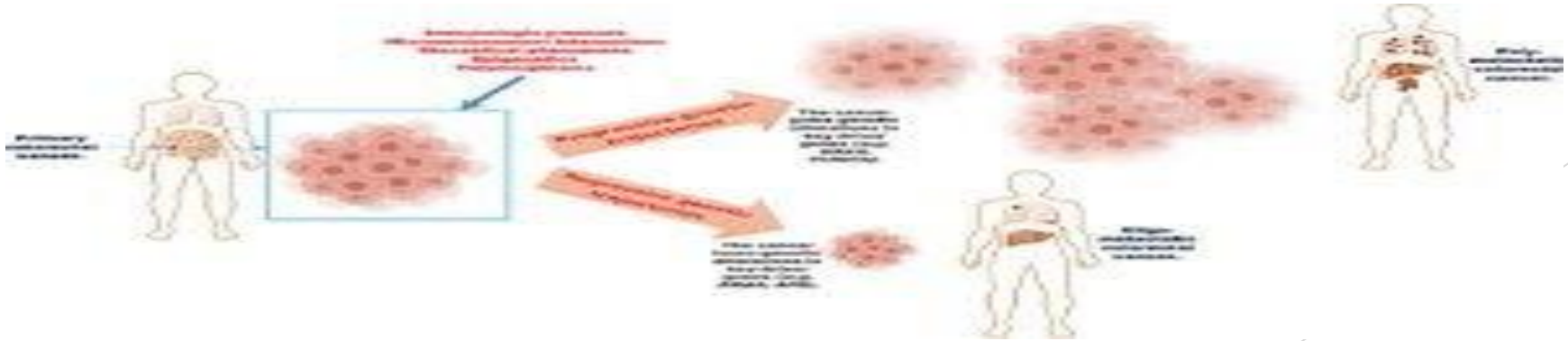


Genetic trajectories underlying the different behavior among oligo- and poly-metastatic CRC.
The figure represents two clinical models previously studied
A) Patients without recurrence at 3-year follow-up
B) patients whose cancer recurred within 1 year after resection of the primary colorectal cancer and the single liver metastatic lesion.



A “regressive” genetic trajectory was intended as the loss of the genetic alterations in a specific gene from the primary tumor to the metastatic one mutant KRAS in primary tumor wild-type KRAS in metastases;
this issue was opposed to “progressive” genetic trajectory where the metastatic lesions gain genetic alterations.

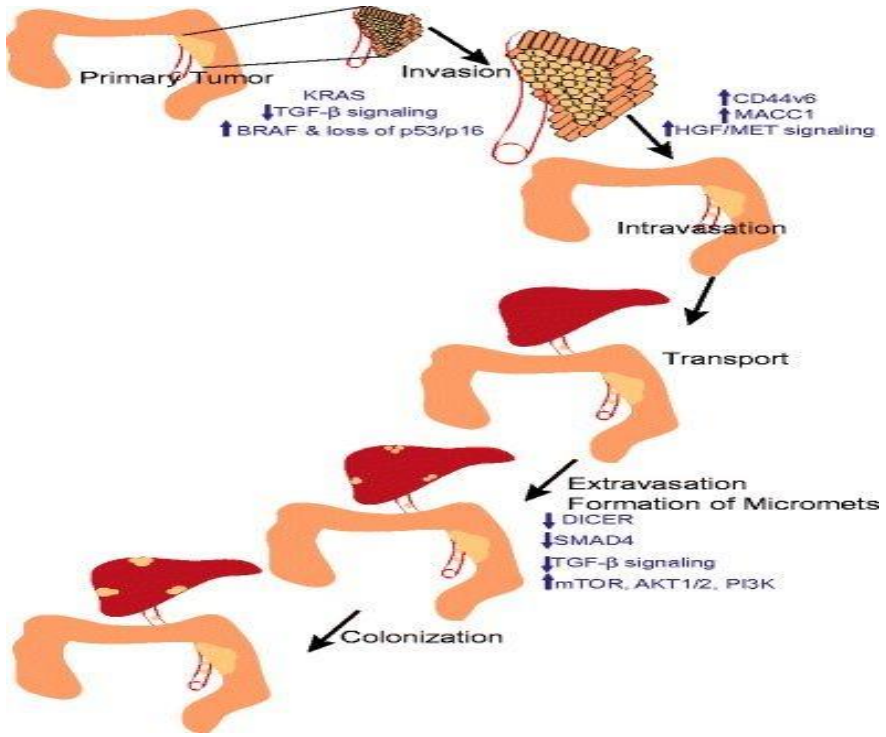
Metastatic CRC genomes were found to be not fundamentally different from primary CRCs in terms of the mutational landscape or of genes that drive tumorigenesis, and a genomic heterogeneity associated with tumor location of primary tumors helps to define different clinical behaviors of metastatic CRCs. Although CRC metastatic spreading was traditionally seen as a late-occurring event, growing evidence suggests that this process can begin early during tumor development and the clonal architecture of these tumors is consistently influenced by cancer treatment. Although the survival rate of patients with metastatic CRC patients improved in the last years, the response to current treatments and prognosis of many of these patients remain still poor, indicating the need to discover new improvements for therapeutic vulnerabilities and to formulate a rational prospective of personalized therapies.



Uncontrollable metastatic outgrowth process is the leading cause of mortality worldwide, even in the case of colorectal cancer.

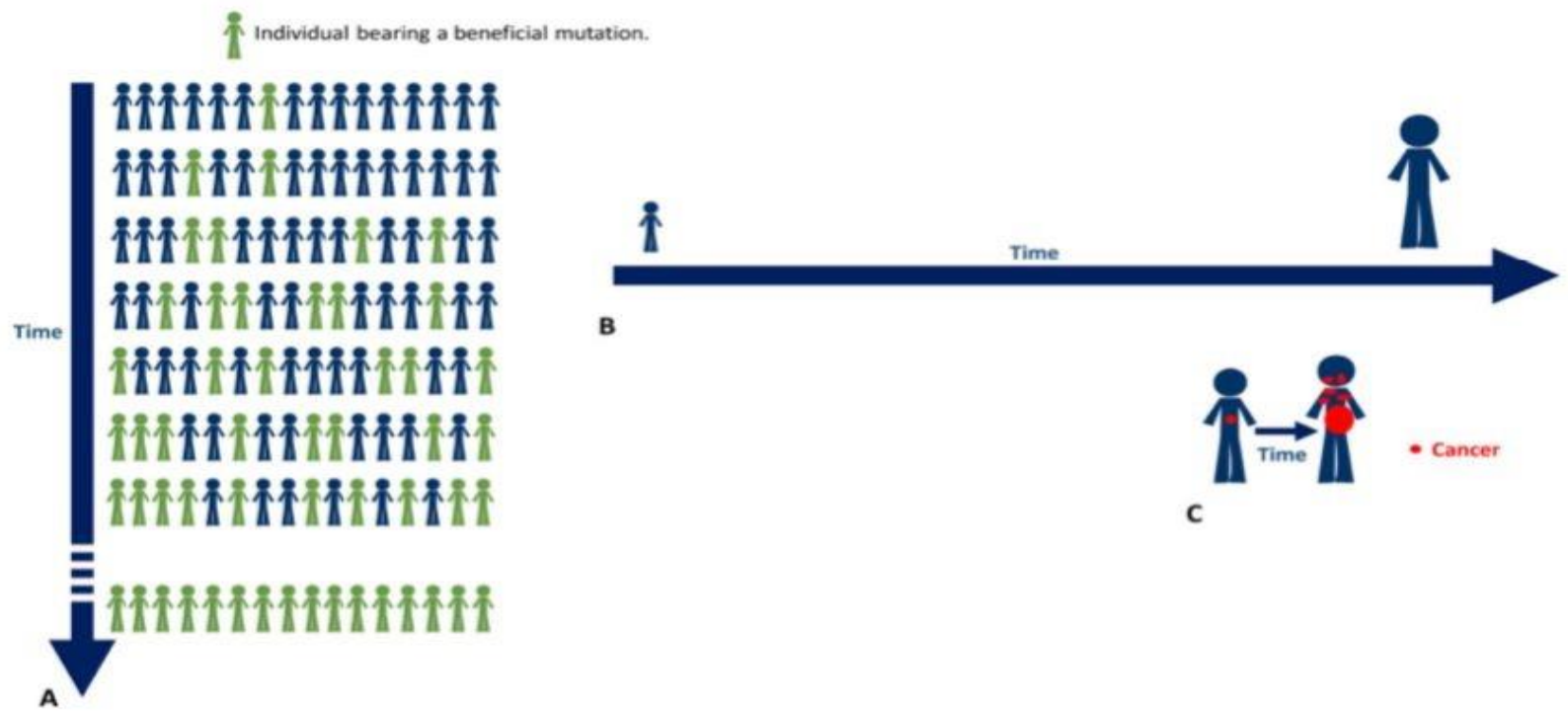
Colorectal cancer (CRC) accounts for approximately 10% of all annually diagnosed cancers and 50% of CRC patients will develop metastases in the course of disease.

Most patients with metastatic CRC have incurable disease. Even if patients undergo resection of liver metastases.



The time to fix a single beneficial mutation in a condition of stable environment and no back mutations is about 1000 generations equivalent to about 25,000 years. B.

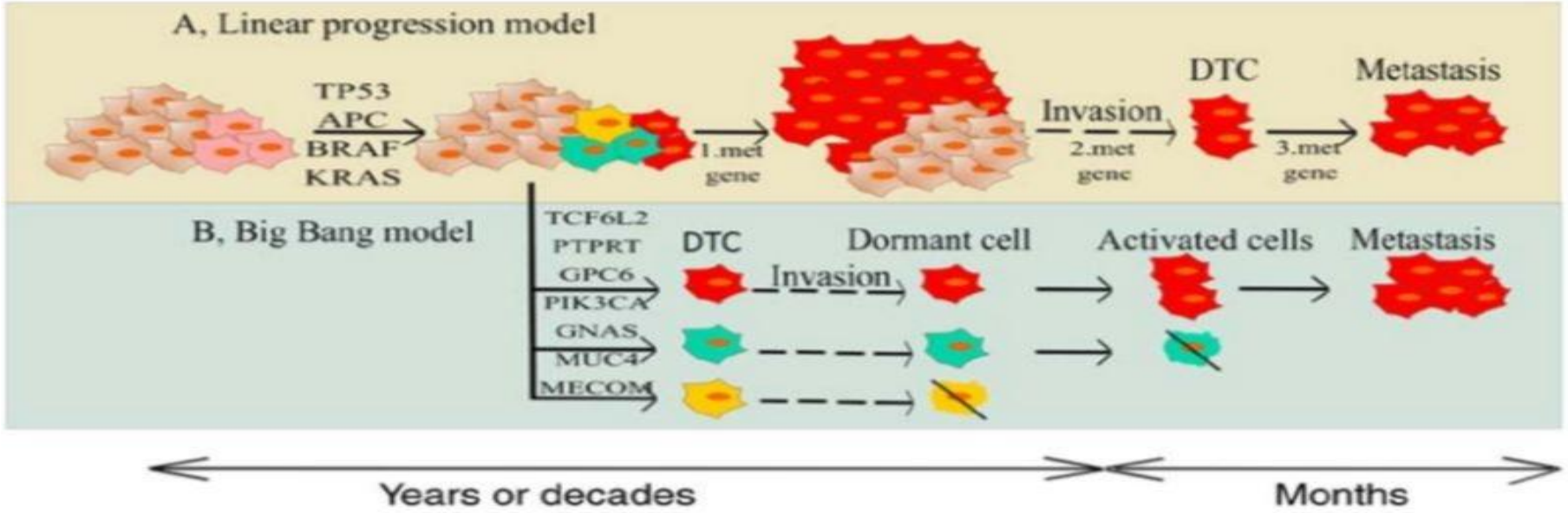
The average life span of humans is about 75 years. C. The evolution of CRC from the precursor to the full and clinical evident malignant progeny is about 5–15 years.



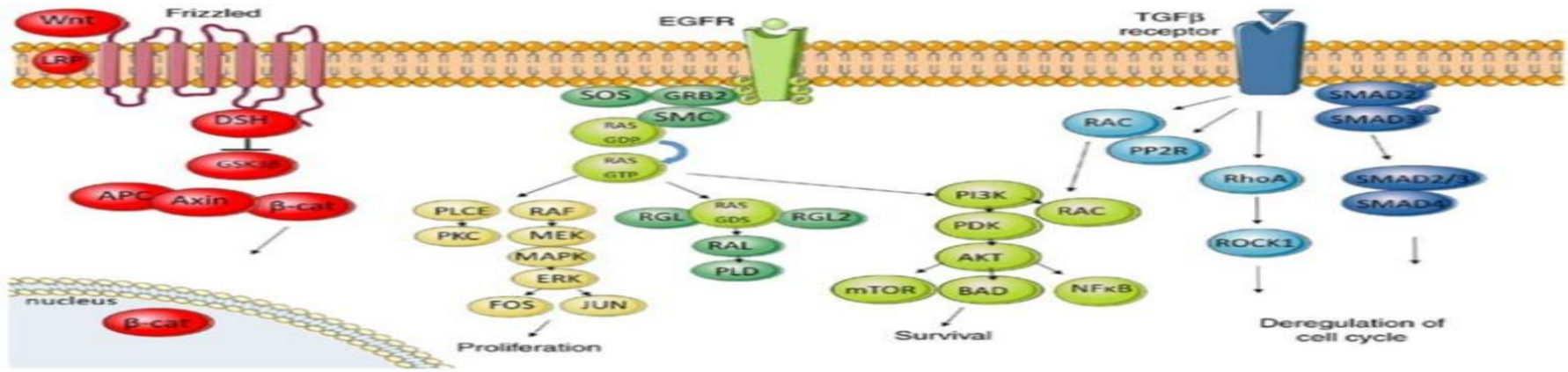
Two models regarding gaining metastatic competence:

(A) The first model is the concept of transition of initiated cell to more aggressive state and gaining of metastatic ability due to the accumulation of genetic and epigenetic changes.

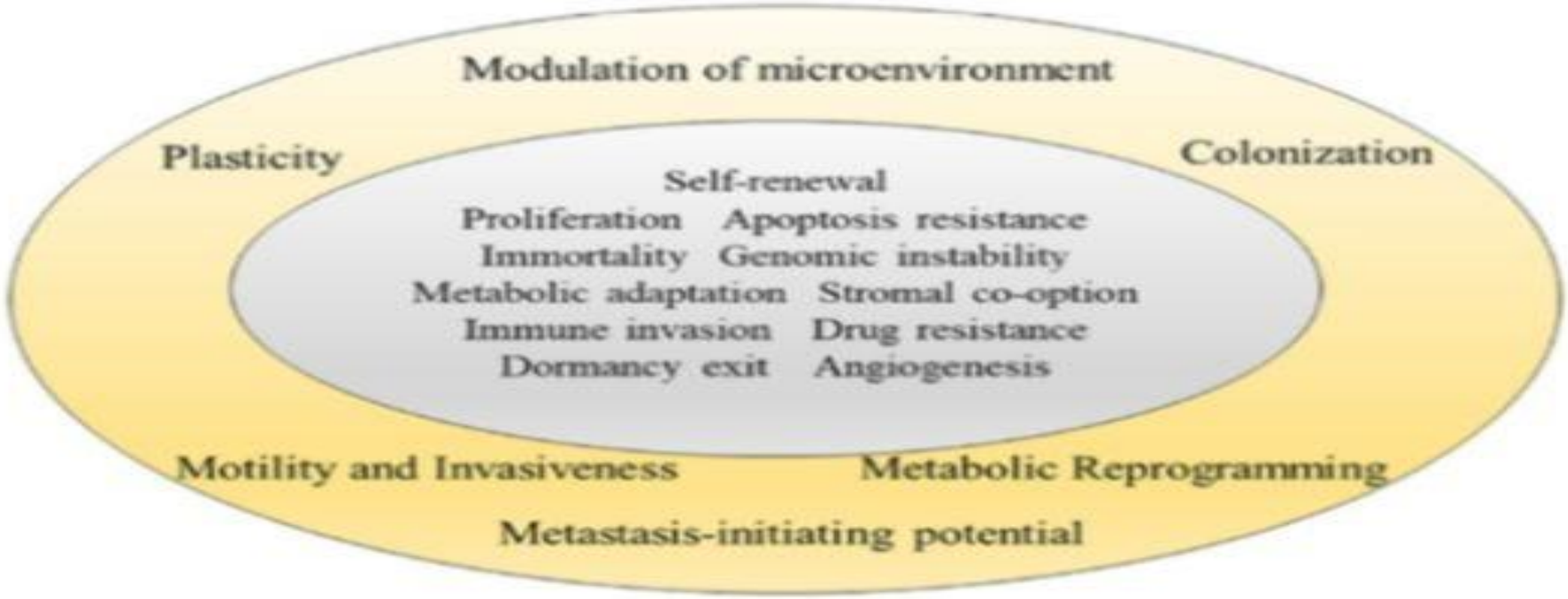
(B) The second model explains that there are some clones in tumor bulk with metastatic potential already present in early stages of carcinogenesis and their individual gene signature is predictive for the invasiveness and distant recurrence. APC, adenomatous polyposis coli; CIN, chromosome instability; DTC, dormant tumor cells; MSI, microsatellite instability; SMAD4, mothers against decapentaplegic homolog 4; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TCF7L2, transcription factor 7-like 2; AMER1, APC membrane recruitment protein 1; PTPRT, Receptor-type tyrosine-protein phosphatase T; GNAS, heterotrimeric G-protein alpha subunit GsFXR1, fragile X mental retardation syndrome-related protein 1; MUC4, Mucin 4; GPC6, Glypican-6; MECOM, MDS1 and EVI1 complex locus protein EVI1.



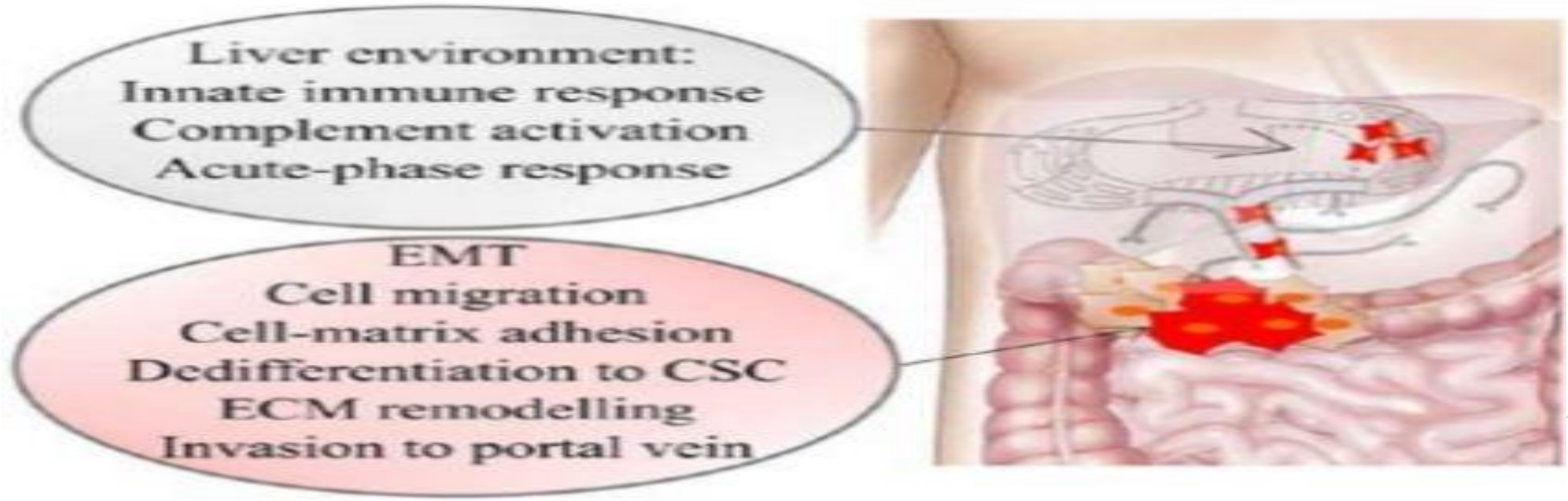
Signaling pathways that drive or enhance CRC metastasis.
For WNT/ß-catenin, Wnt-ligands , Respondin-ligands or alteration in function of APC or ß-catenin lead to the integral activation of canonical WNT signaling leading to the transfer of ß-catenin from the cytoplasm to the nucleus.
Higher cellular stem- ness and proliferation together with a rise of motility and polarity are associated with activation of WNT signaling.
Regarding the EGFR pathways, transformed cells accumulate constitutively active RAS proteins able to trigger downstream signaling even in the absence of extracellular signal. RAS recruits and activates several downstream effectors in different pathways: PI3K-AKT and MAPK/ERK pathways and the cascade comprising RAF kinase.
All pathways contribute to the control of cell growth, differentiation, and survival. For TGF-ß signaling , activation through TGF-ß receptors results in SMAD2 and SMAD3 phosphorylation and binding to SMAD4. The complex is translocated into the nucleus to regulate the transcription of the target genes. Loss of SMAD2 and SMAD4 leads to an ability to evade apoptosis and deregulation of the cell cycle. TGF-ß activation turns on also MAPK pathways, PI3K, Notch and WNT signaling.



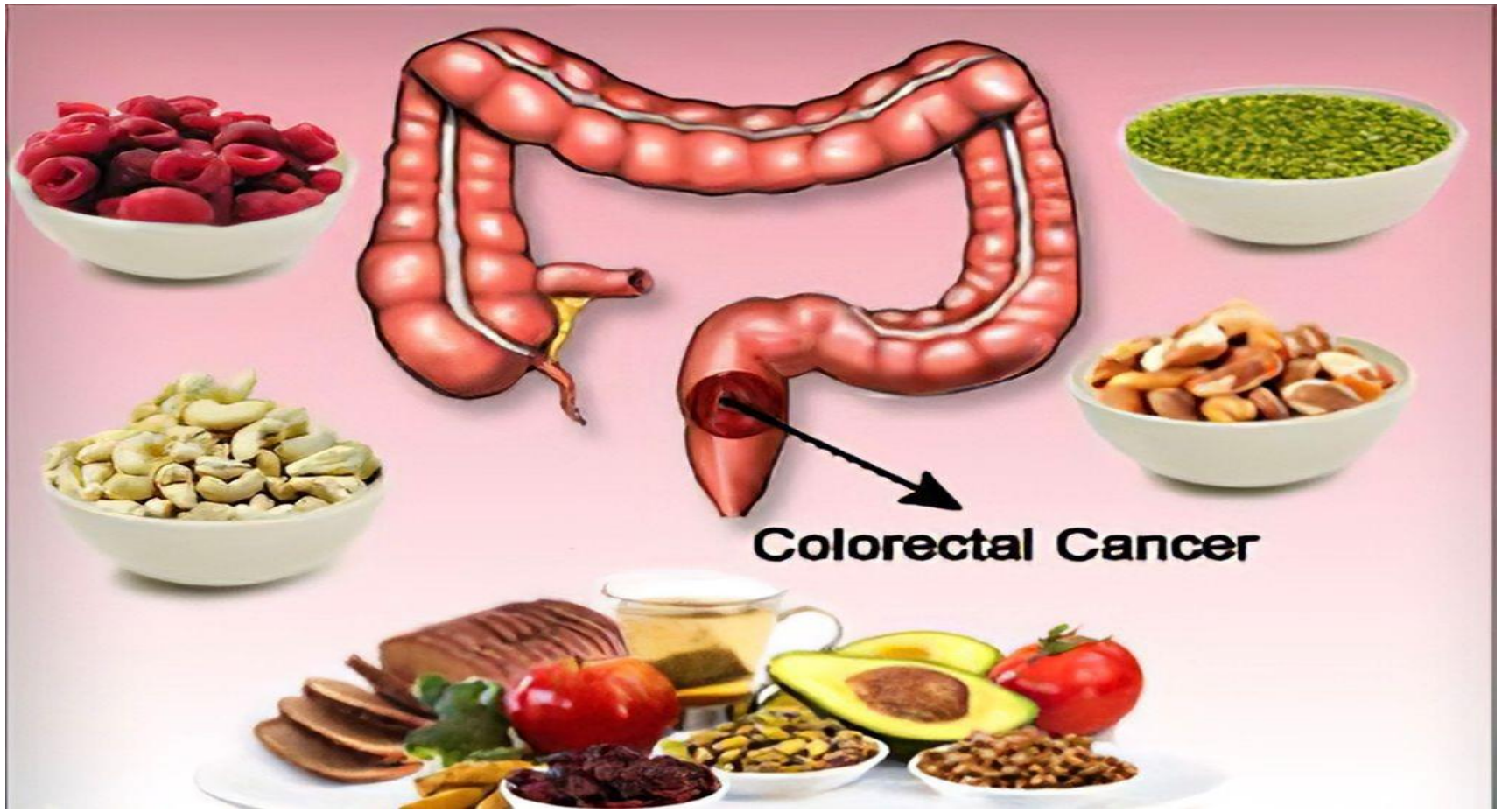
The hallmarks of metastatic cells.
Metastatic cells keep all essential ‘hallmarks of cancer’ (the core of the image) and expand them by acquiring certain traits (the periphery of the picture):Plasticity, motility and invasion, capability to modulate the local microenvironments and the ability to colonize secondary tissues. Prior to becoming metastatic,
the cells lose the capacity to fully differentiate ; they are not inhibited by cell-cell contact; they are not anchorage-dependent; and are genetically unstable.



Metastatic spreading to the liver. Disseminating cells are subjected to EMT and dedifferentiation into cells with stem-like properties so as to gain the migratory ability. After ECM remodeling ,they left the vascular system and invaded the liver through the portal vein.
The primary tumor itself actively supports preparation of the pre metastatic niche by the activation of inflammatory and immune cells involving CAFs, neutrophils, macrophages and TAMs subtype 1.
CAF, carcinoma-associated fibroblasts; TAM, tumor associated macrophage; ECM, extracellular matrix.



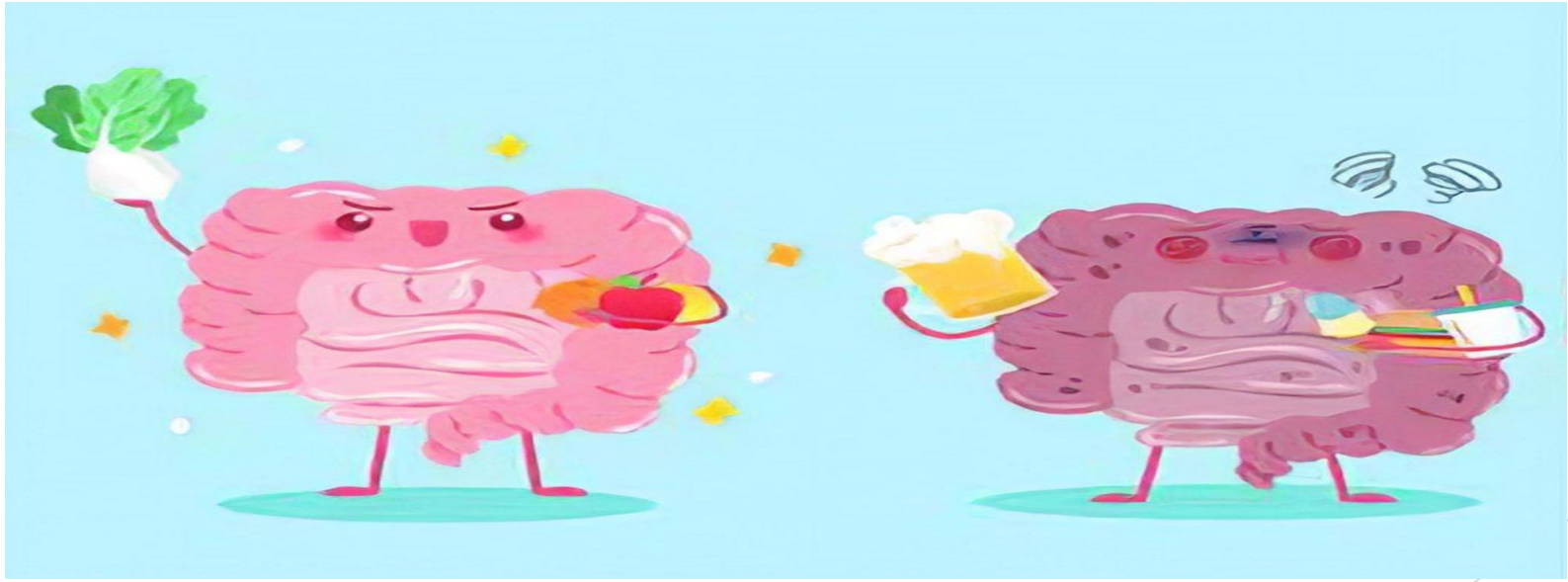
Diet at risk for bowel cancer



Diet is a significant contributor to colon cancer risk.
The following factors are associated with reduced risk of colorectal cancer : Maintaining a healthy weight .

A meta-analysis of observational studies, including more than 16,000 cases, concluded that for every 5 kg of weight gained during adulthood, the risk for colorectal cancer increased by 4%. For a weight gain of roughly 30lbs , the risk increased by 22%, compared with individuals who had maintained weight.

Compared with individuals who were healthy weight or slightly overweight, both obese and underweight patients had significantly weaker cancer-specific and overall mortality, while underweight patients also had significantly higher disease recurrence and lower disease-free survival.



Consuming a healthful dietary pattern. In the Adventist Health Study, including nearly 100,000 women and men, those avoiding meat and fish consumption had significantly lower risk, compared with those following omnivorous diets .

A systematic review and meta-analysis of primary prevention cohort studies found that greater adherence to a Mediterranean dietary pattern was associated with a roughly 10% lower risk for colorectal cancer, and a systematic review and meta-analysis of observational studies found a 17% lower risk .

In the Women's Health Initiative Observational Study, greater adherence to either the Dietary Approaches to Stop Hypertension (DASH) or the Healthy Eating Index (HEI-2010) diets was inversely associated with the risk for colorectal cancer.

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THANK YOU
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