# Cancer Susceptibility

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Cancer

- All cancers derive from single cells that have acquired the characteristics of continually dividing in an unrestrained manner and invading surrounding tissues.

- Cancer cells behave in this abnormal manner because of changes in the DNA sequence of key genes, which are known as cancer genes (oncogenes, tumor suppressor genes and DNA repair genes).

- All cancers are genetic diseases.

- There are approximately 200 types of cancer, each with different causes, symptoms and treatments.
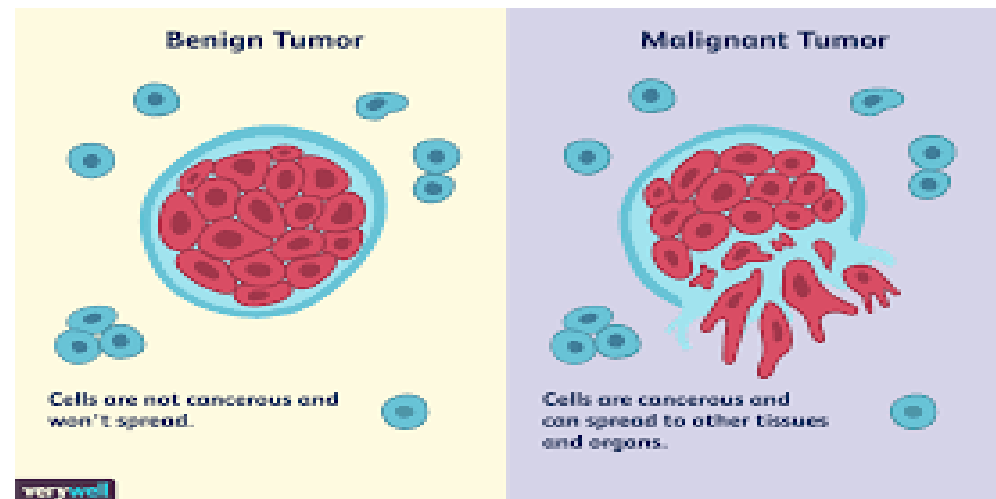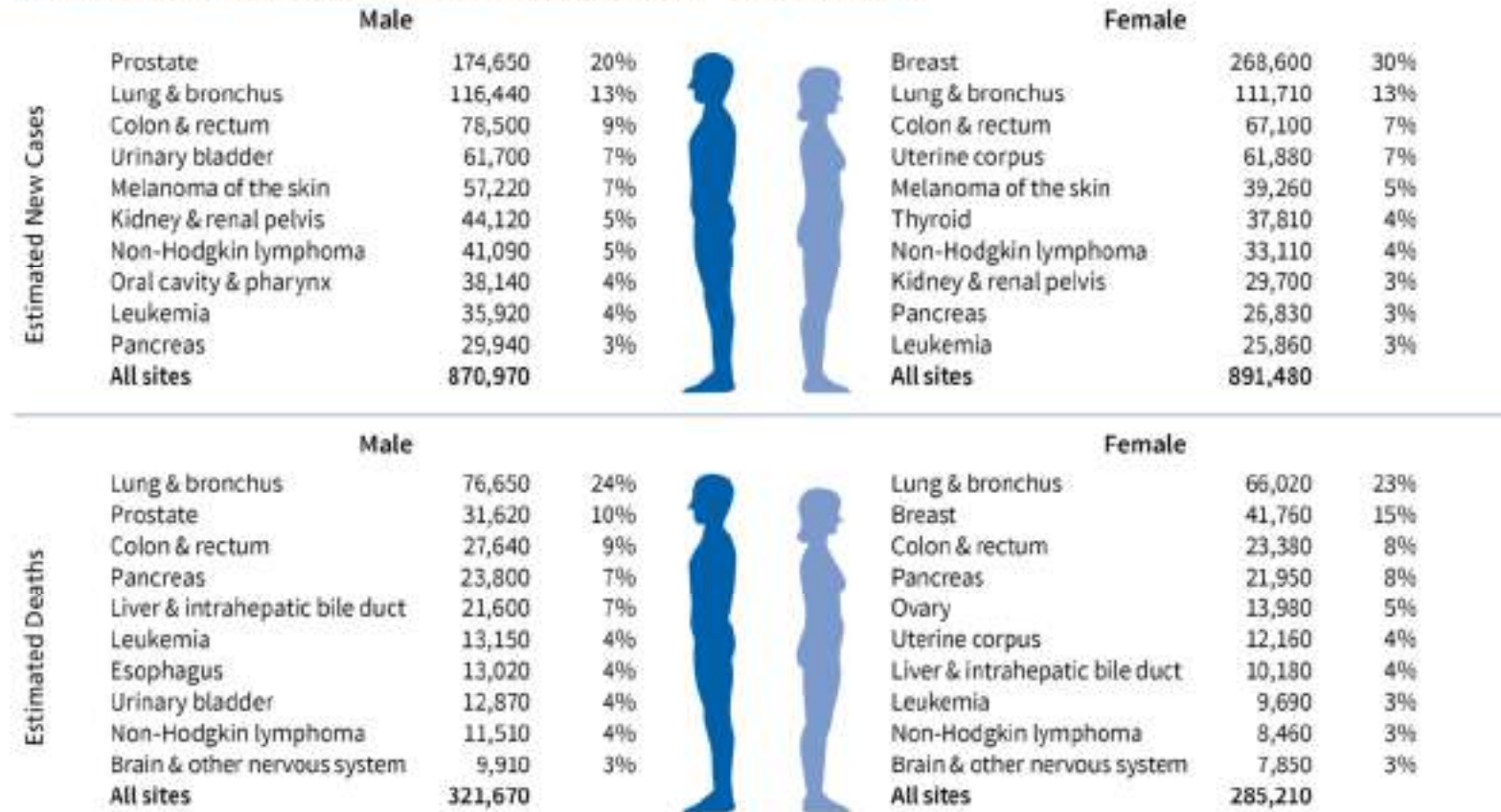
The Hallmarks of Cancer
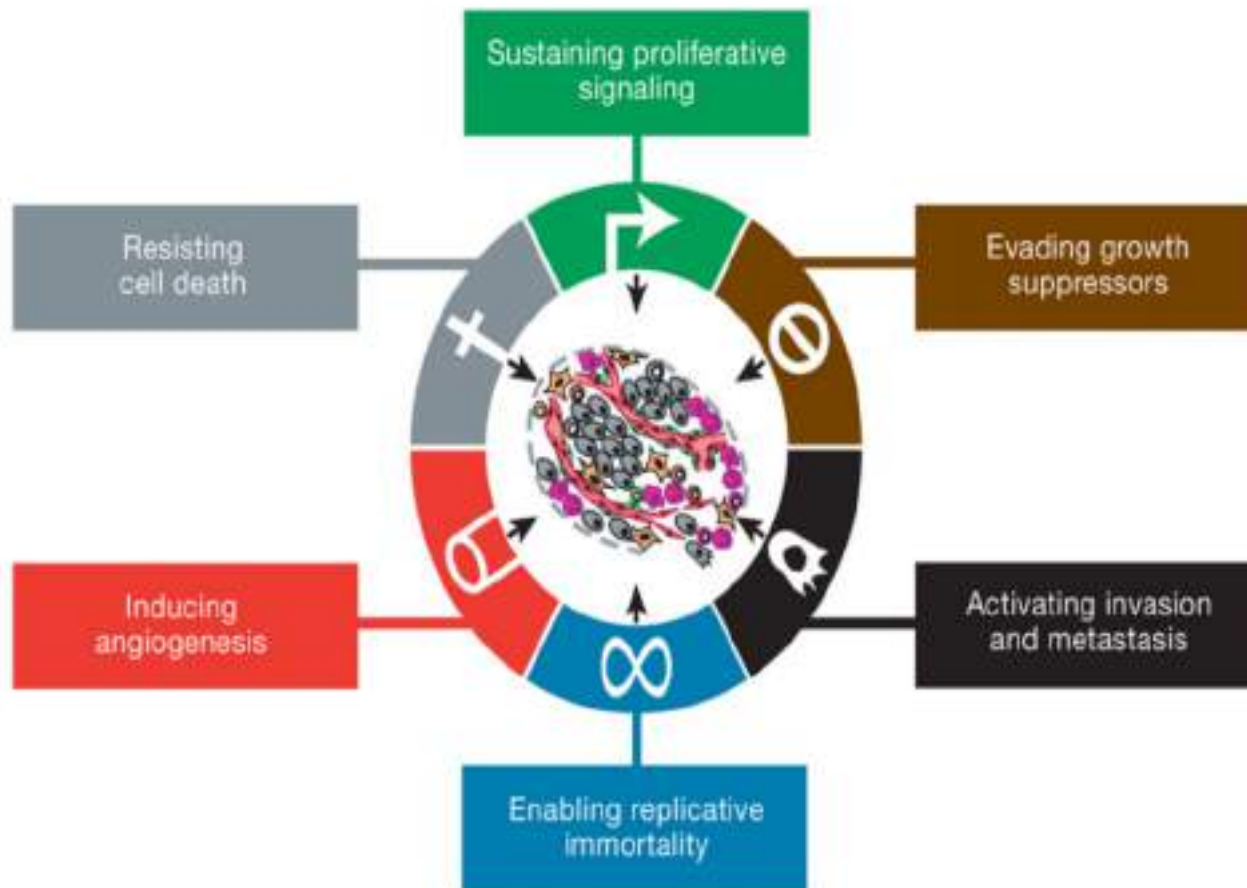
- Sustained proliferative signaling (activation of Ras or myc oncogenes)

- Evading growth suppressors (inactivation of tumor suppressor genes-Rb)

- Activating invasion and metastasis (cadherin etc)

- Enabling replicative immortality

- Inducing angiogenesis (angiogenic activators protein-TNF,FGF VEGF,)
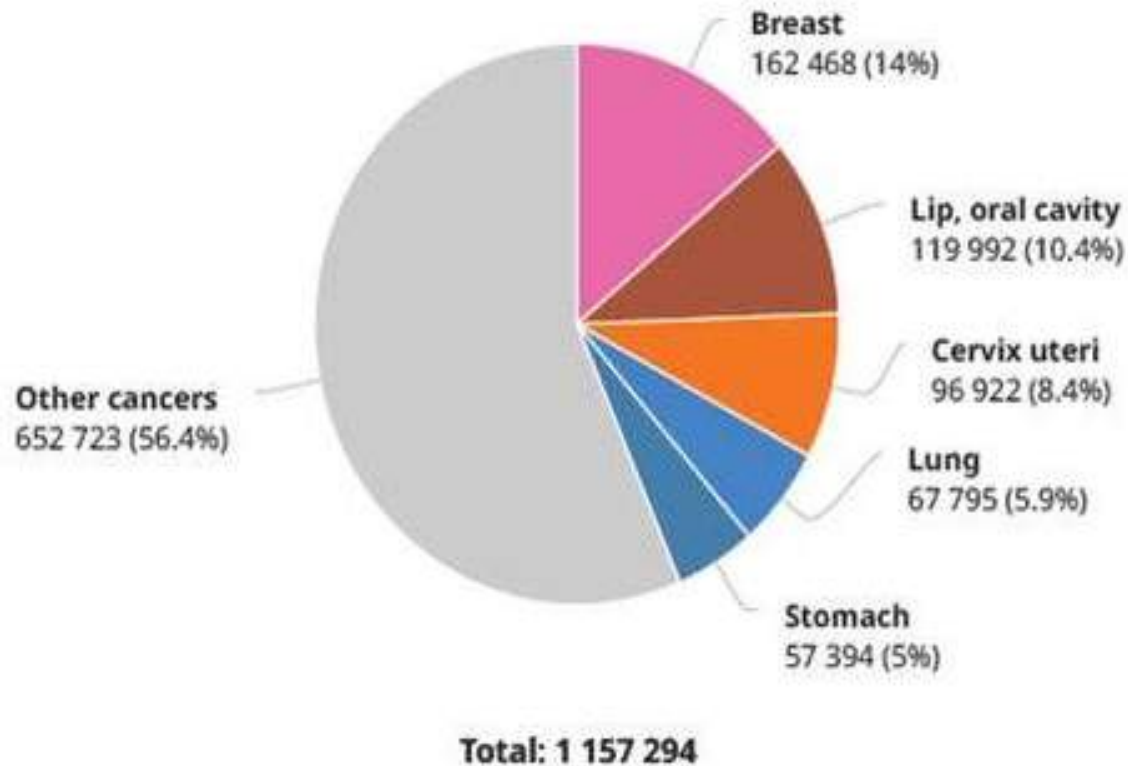
- Resisting cell death

Cancer

Cancer is a leading cause of death worldwide, accounting for an estimated 9.6 million deaths in 2018.

Figure 3. Leading Sites of New Cancer Cases and Deaths – 2019 Estimates

Estimated New Cases

Male				Female		
Prostate	174,650	20%		Breast	268,600	30%
Lung & bronchus	116,440	13%		Lung & bronchus	111,710	13%
Colon & rectum	78,500	9%		Colon & rectum	67,100	7%
Urinary bladder	61,700	7%		Uterine corpus	61,880	7%
Melanoma of the skin	57,220	7%		Melanoma of the skin	39,260	5%
Kidney & renal pelvis	44,120	5%		Thyroid	37,810	4%
Non-Hodgkin lymphoma	41,090	5%		Non-Hodgkin lymphoma	33,110	4%
Oral cavity & pharynx	38,140	4%		Kidney & renal pelvis	29,700	3%
Leukemia	35,920	4%		Pancreas	26,830	3%
Pancreas	29,940	3%		Leukemia	25,860	3%
All sites	870,970			All sites	891,480	

Estimated Deaths

Male				Female		
Lung & bronchus	76,650	24%		Lung & bronchus	66,020	23%
Prostate	31,620	10%		Breast	41,760	15%
Colon & rectum	27,640	9%		Colon & rectum	23,380	8%
Pancreas	23,800	7%		Pancreas	21,950	8%
Liver & intrahepatic bile duct	21,600	7%		Ovary	13,980	5%
Leukemia	13,150	4%		Uterine corpus	12,160	4%
Esophagus	13,020	4%		Liver & intrahepatic bile duct	10,180	4%
Urinary bladder	12,870	4%		Leukemia	9,690	3%
Non-Hodgkin lymphoma	11,510	4%		Non-Hodgkin lymphoma	8,460	3%
Brain & other nervous system	9,910	3%		Brain & other nervous system	7,850	3%
All sites	321,670			All sites	285,210	

Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Estimates do not include Puerto Rico or other US territories. Ranking is based on modeled projections and may differ from the most recent observed data.

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India (Globocan 2018)

Breast
162 468 (14%)

Lip, oral cavity
119 992 (10.4%)

Cervix uteri
96 922 (8.4%)

Other cancers
652 723 (56.4%)

Lung
67 795 (5.9%)

Stomach
57 394 (5%)

Total: 1 157 294

Cancer type	Incidence in 2018	%
Breast cancer	162468	14%
Lip and oral Cavity	119992	10.4%
Cervix uteri	67795	5.9%
Stomach	57394	5%
others	652723	56.4%
Total	1,157294	

Number of new cases in 2018 in both sexes

MethylenetetrahydrofolateReductase (MTHFR)

One of the most critical enzymes involved in **folate metabolism**.

- It irreversibly catalyzes the conversion of **5,10-methylenetetra hydrofolate to 5-methyltetra hydrofolate(5-THF).**

- 5-THF donates methyl group for the conversion of **homocysteine** to **methionine,** which is further converted into **S-adenosylmethionine(SAM).**

- **SAM** is the main methyl group donor for all cellular methylation reactions.

- **Human MTHFR enzyme is a 77-kilodalton protein.**
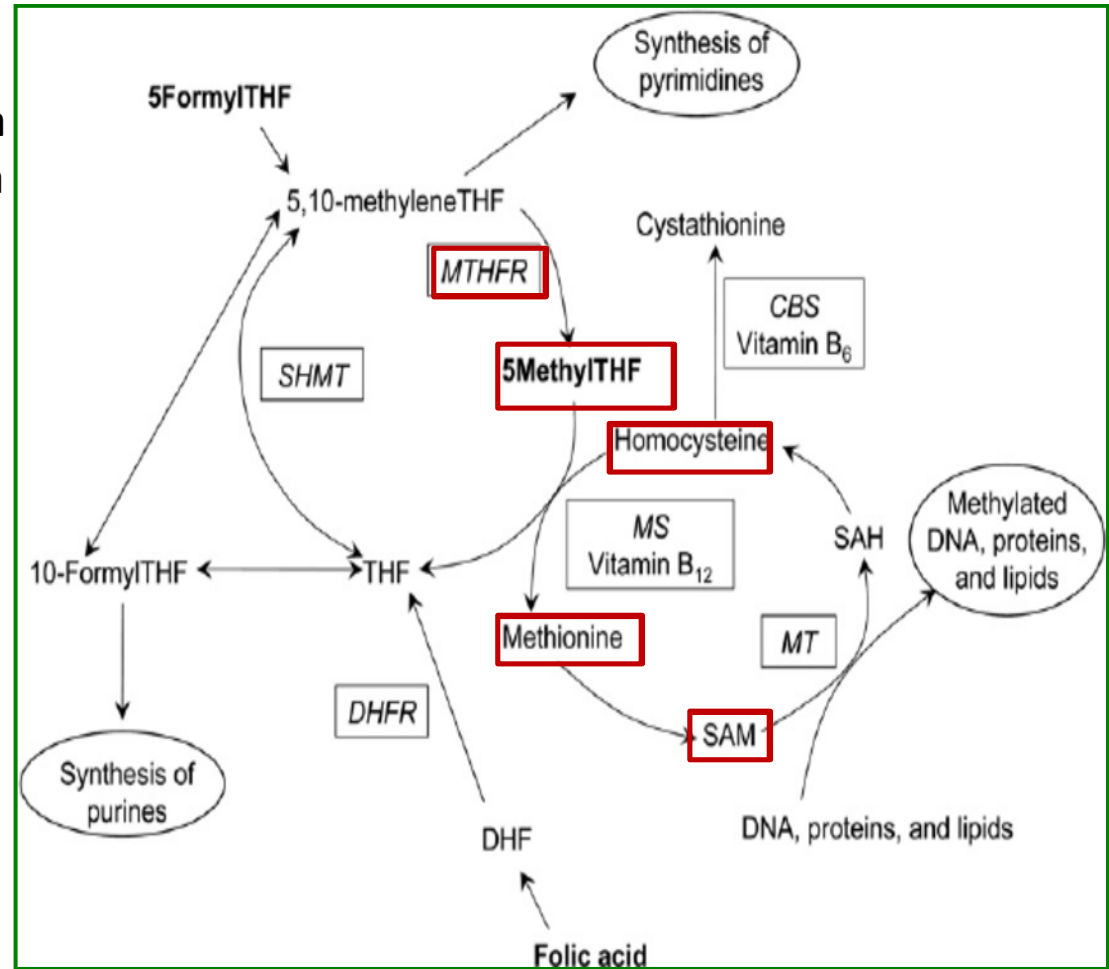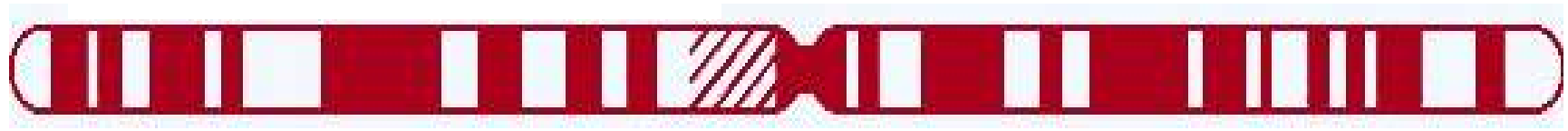
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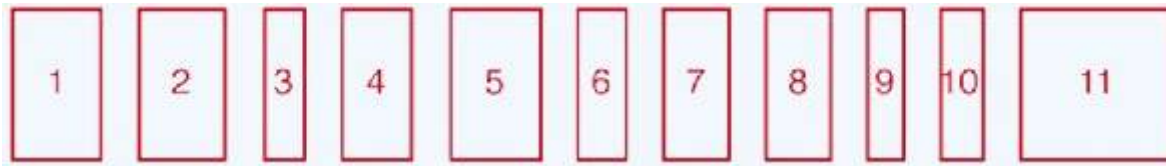
11 Exons

C677T Polymorphism

A1298C Polymorphism

DNA

• TCT GCG GGA GCC GAT TTC ATC..

. TCT GCG GGA GTC GAT TTC ATC..

....ACC AGT GAA GAA AGT GTC TTT..

....ACC AGT GAA GCA AGT GTC TTT..

mRNA

. UCU GCG GGA GCC GAU UUC AUC..

. UCU GCG GGA GUC GAU UUC AUC..

....ACC AGU GAA GAA AGU GUC UUU

....ACC AGU GAA GCA AGU GUC UUU

Protein

.. S A G A D F I.......
(Alanine)
222

.. S A G V D F I.......
(Valine)

.... T S E E S V F...
(Glutamate)
429

..... T S E A S V F...
(Alanine)

ICRALBEH-2019

MTHFR polymorphism and Cancer

Breast Cancer

Esophageal Cancer

Ovarian Cancer

MTHFR
Polymorphism

Lung Cancer

Colorectal cancer

Prostate Cancer
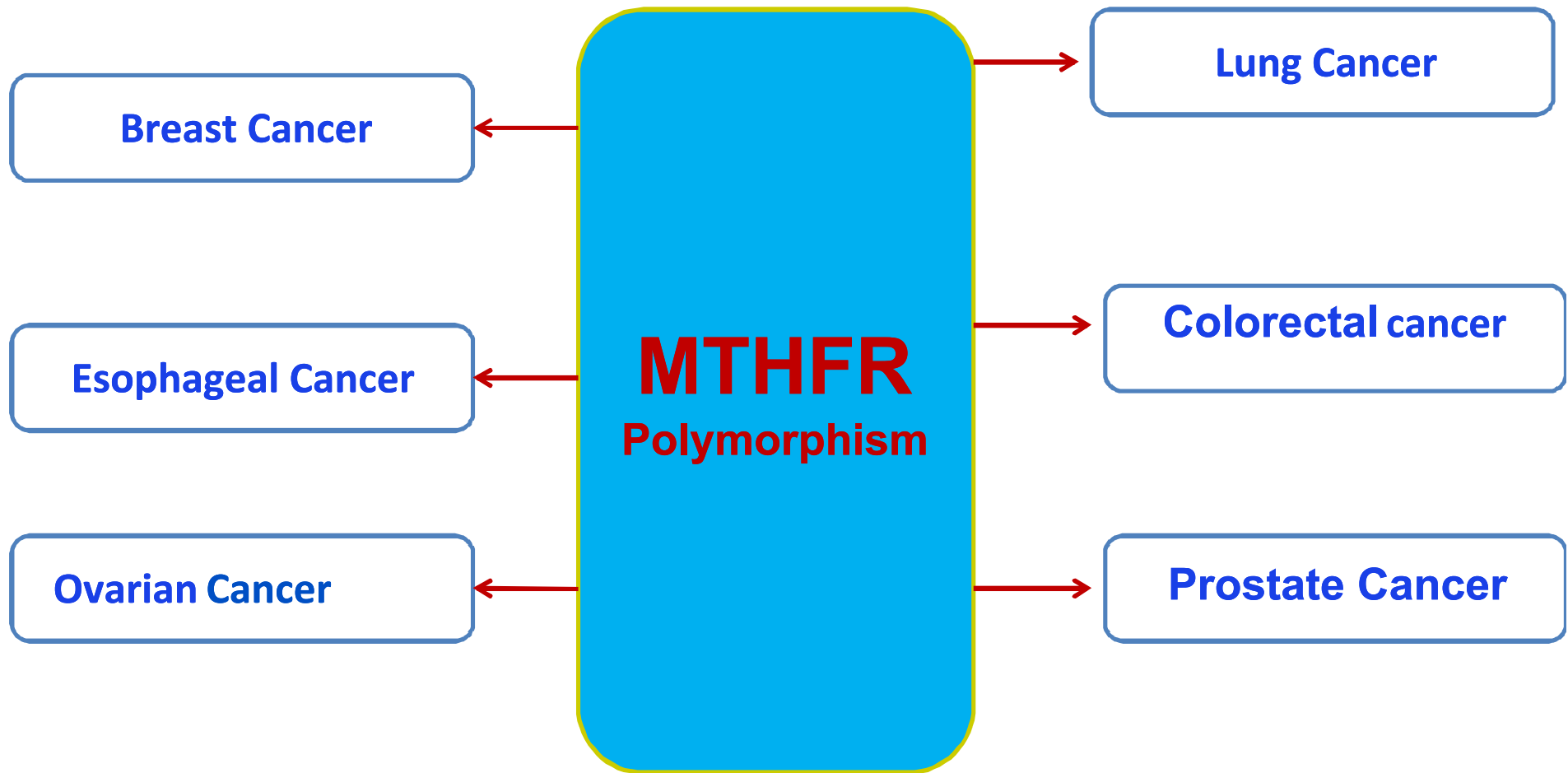
Breast Cancer

(Global incidence-20,88,849; Indian incidence-162468)

Symptoms:

- The first symptoms of breast cancer usually appear as an area of thickened tissue in the breast or a **lump** in the breast or an armpit,

- **Pain in the armpits** or breast that does not change with monthly cycle,

- **Pitting or redness of the skin** of the breast, similar to the surface of the orange,

- A change in the size or shape of the breast, and

- Peeling, flanking or scaling of the skin on the breast or nipples.

Risk Factors:

Age, genetics (BRCA1, BRCA2, p53 etc), family history, alcohol consumption, obesity, hormone treatment etc.

https://gco.iarc.fr/today/data/factsheets/populations/356-india-fact-sheets.pdf

Region	Incidence	Mortality
Australia and New Zealand	94.2	12.6
Western Europe	92.6	15.5
Northern Europe	90.1	14.1
North America	84.8	12.6
Southern Europe	80.3	13.3
Polynesia	70.5	21.6
South America	56.8	13.4
Central and Eastern Europe	54.5	15.5
Caribbean	50.2	18.1
Melanesia	49.7	25.5
Northern Africa	48.9	18.4
World	46.3	13.0
Southern Africa	46.2	15.6
Western Asia	45.3	13.6
Micronesia	42.5	16.3
Eastern Asia	39.2	8.6
Central America	38.3	10.1
South-Eastern Asia	38.1	14.1
Western Africa	37.3	17.8
Eastern Africa	29.9	15.4
Middle Africa	27.9	15.8
South-Central Asia	25.9	13.6

ASR (World) per 100 000

MTHFR and Breast Cancer

RESEARCH ARTICLE

The Methylenetetrahydrofolate Reductase C677T Polymorphism and Breast Cancer Risk in Asian Populations

Vandana Rai

OR (95%CI),p
TT vs. CC: OR= 1.17, (1.06–1.28), 0.001
Association=Yes

Meta Gene 6 (2015) 72–84

Contents lists available at ScienceDirect

Meta Gene

ELSEVIER

META GENE

Methylenetetrahydrofolate reductase gene C677T polymorphism and breast cancer risk: Evidence for genetic susceptibility
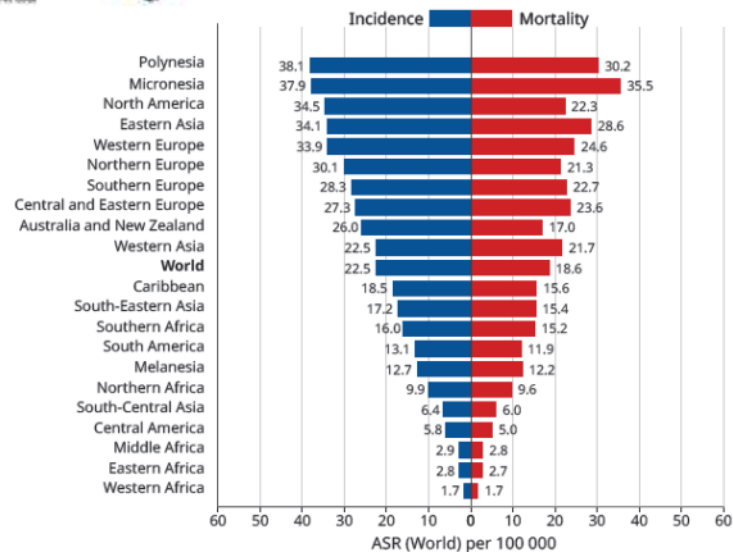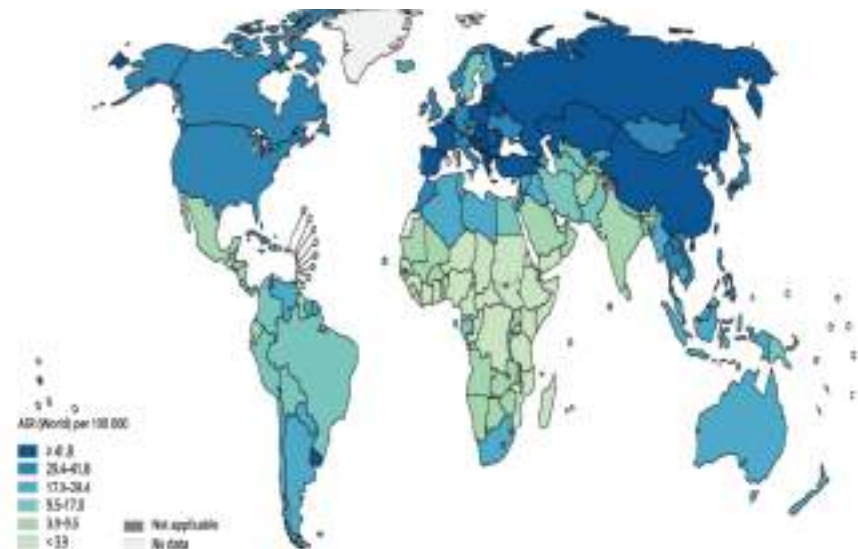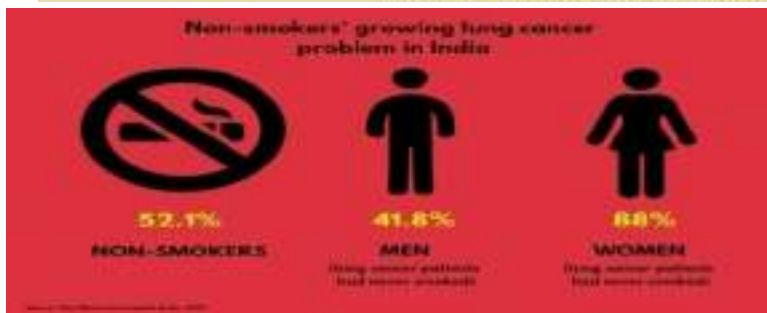
CrossMark

Pradeep Kumar, Upendra Yadav, Vandana Rai *

Human Molecular Genetics Laboratory, Department of Biotechnology, VBS Purvanchal University, Jaunpur 222 003, UP, India

Lung Cancer

2093876; India -67795)

SYMPTOMS

COUGH

VOICE CHANGES

COUCH TO BLOOD

WHEEZING

CHEST PAIN

WEIGHT LOSS

RISK FACTORS

FAMILY HISTORY

EXPOSURE TO RADON GAS

SMOKING

EXPOSURE TO SECONDHAND SMOKE

Non-smokers' growing lung cancer problem in India

52.1%
NON-SMOKERS

41.8%
MEN

88%
WOMEN

https://gco.iarc.fr/today/data/factsheets/populations/356-india-fact-sheets.pdf

	Incidence	Mortality
Polynesia	38.1	30.2
Micronesia	37.9	35.5
North America	34.5	22.3
Eastern Asia	34.1	28.6
Western Europe	33.9	24.6
Northern Europe	30.1	21.3
Southern Europe	28.3	22.7
Central and Eastern Europe	27.3	23.6
Australia and New Zealand	26.0	17.0
Western Asia	22.5	21.7
World	22.5	18.6
Caribbean	18.5	15.6
South-Eastern Asia	17.2	15.4
Southern Africa	16.0	15.2
South America	13.1	11.9
Melanesia	12.7	12.2
Northern Africa	9.9	9.6
South-Central Asia	6.4	6.0
Central America	5.8	5.0
Middle Africa	2.9	2.8
Eastern Africa	2.8	2.7
Western Africa	1.7	1.7

ASR (World) per 100 000

Incidence and mortality rate of lung cancer in 2018

MTHFR and Lung Cancer

RESEARCH ARTICLE

Folate Pathway Gene MTHFR C677T Polymorphism and Risk of Lung Cancer in Asian Populations

Vandana Rai

OR (95%CI),p
TT vs CC: OR=1.25 (1.01-1.30), <0.0001
Association=Yes

Esophageal Cancer (ECa)
(Global incidence -572034; India-33890)

Symptoms:

Weight loss,

indigestion,

heartburn,

pain or difficulty in swallowing,

frequent choking while eating,

vomiting,

food coming back up to esophagus,

chest pain,

fatigue, hiccup and chronic cough.

Risk factors:

Alcohol consumption,

smoking,

having reflux disorder (gastroesophageal reflux disease(GERD)),

having Barrett's esophagus (which is a condition characterized by damaged esophageal lining due to GERD being overweight).

https://gco.iarc.fr/today/data/factsheets/populations/356-india-fact-sheets.pdf
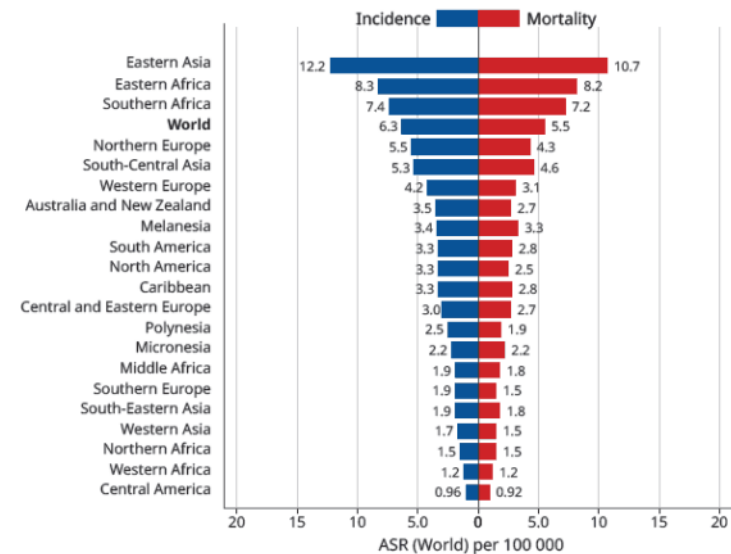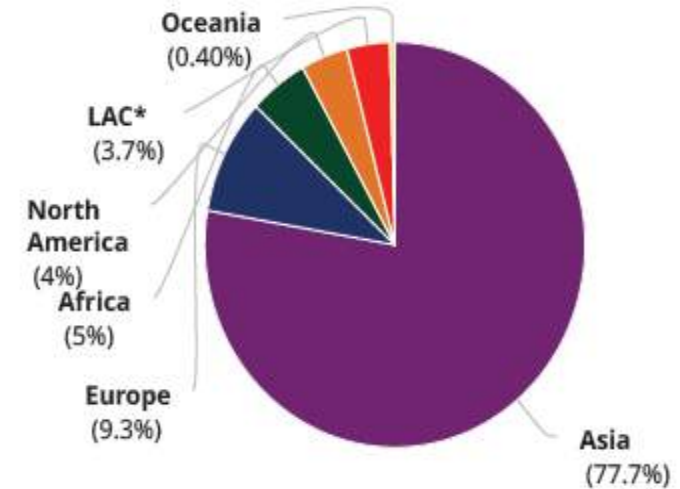
Incidence and mortality rate of ECa in 2018

MTHFR and Esophageal Cancer

Review

MTHFR C677T polymorphism and risk of esophageal cancer: An updated meta-analysis

Pradeep Kumar, Vandana Rai [*]

Human Molecular Genetics Laboratory, Department of Biotechnology, VBS Purvanchal University, Jaunpur 222 003, UP, India

 OR (95%CI),p
TT vs. CC : OR=1.37(1.14–1.62),0.0004
Association=Yes
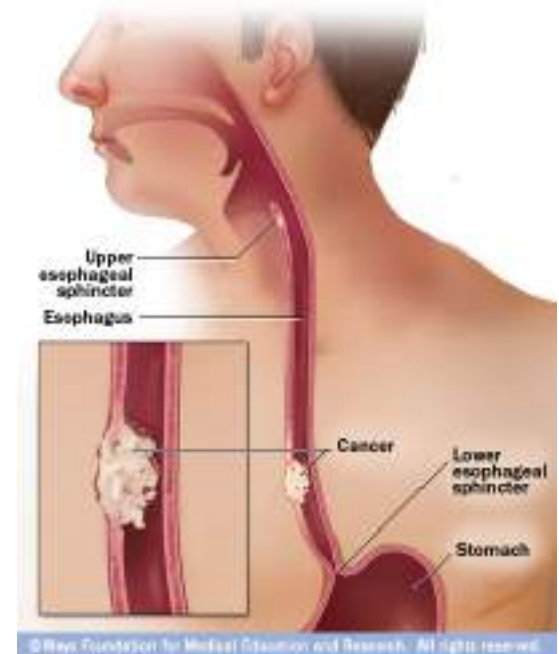
Colorectal Cancer

(Global incidence-1849518; India- 96922)

Colorectal cancer (CRC), also known as bowel cancer, colon cancer or rectal cancer is development of cancer from the colon or rectum (parts of large intestine).

Risk factors are

Old age, obesity, smoking, dietary factors (red meat, processed meat and alcohol)

diseases (inflammatory bowels disease /Crohn's disease and ulcerative colitis) and

inherited genetic disorders like familial adenomatous polyposis and hereditary non-polyposis colon cancer etc.

The warning signs include-

Worsening constipation

blood in stool

decrease in stool caliber (thickness)

loss of appetite

loss of weight and nausea or vomiting.
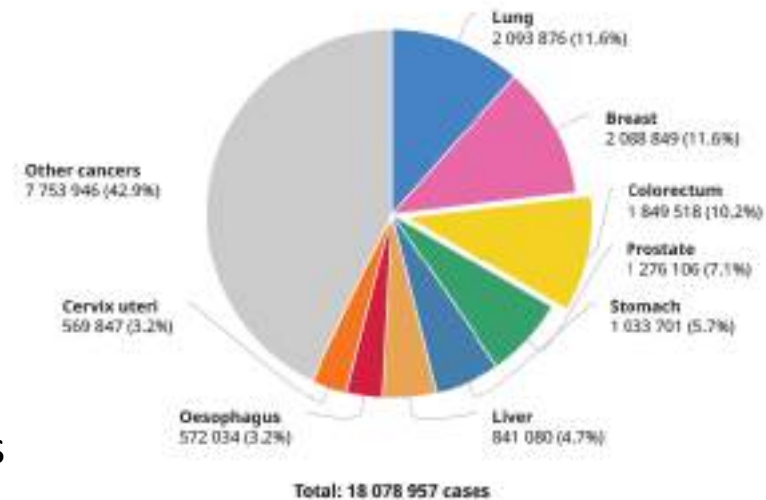
New CRC cases in 2018
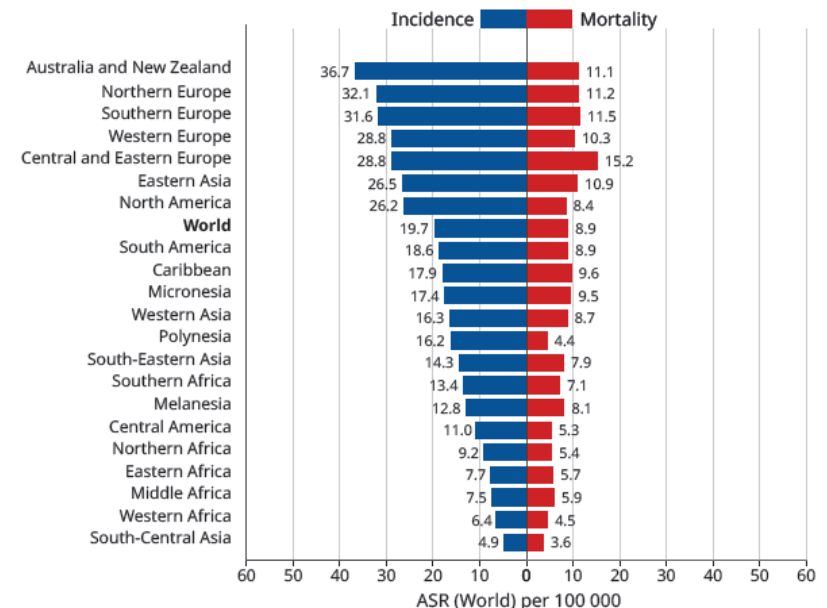
Incidence and mortality rate of CRC in 2018

RESEARCH ARTICLE

Evaluation of the MTHFR C677T Polymorphism as a Risk Factor for Colorectal Cancer in Asian Populations

Vandana Rai

OR (95%CI),p
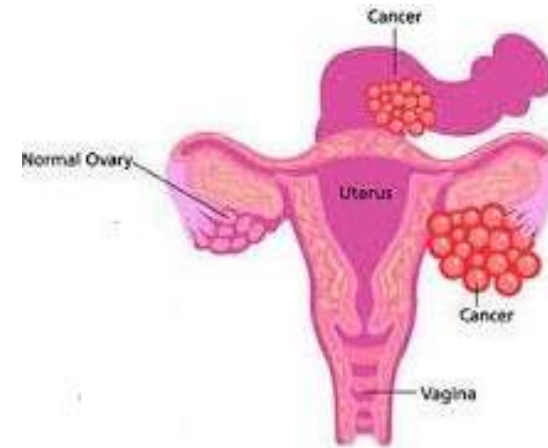T vs. C : OR=0.94(0.90-0.98),0.001
Association= No

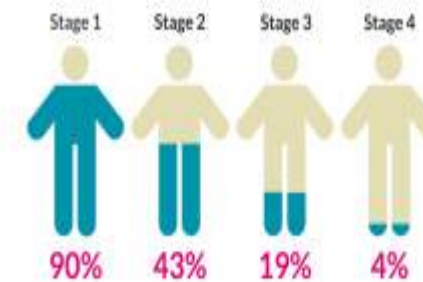# Ovary Cancer

(Global incidence-295414; India-36170)

Tumor marker	Ovarian neoplasm
CA-125	Epithelial ovarian cancer
CEA	Mucinous ovarian cancer
HCG	Embryonal carcinoma Choriocarcinoma
Inhibin A or inhibin B	Granulosa cell tumor
Lactate dehydrogenase	Dysgerminoma
α-Fetoprotein	Endodermal sinus tumor Embryonal carcinoma

Abbreviations: CEA, carcinoembryonic antigen; HCG, human chorionic gonadotropin.

https://in.pinterest.com/pin/643944446689515871/

https://www.thailandmedical.news/news/new-procedure-to-detect-ovarian-cancer-at-an-earlier-curable-stage

OVARIAN CANCER
by race and ethnicity*

11.5 — White
10.3 — Hispanic
9.2 — Black
9.1 — Asian/Pacific Islander
8.3 — American Indian/Alaska Native

*Rate per 100,000 individuals
Source: Centers for Disease Control and Prevention (CDC)

healthli

Stage 1 — 90%
Stage 2 — 43%
Stage 3 — 19%
Stage 4 — 4%

Five-Year Relative Survival (%) by Stage, Adults Aged 15-99, Former Anglia Cancer Network

Review Article   **Open Access**

Methylenetetrahydrofolate Reductase Gene C677T Polymorphism and Its Association with Ovary Cancer

Vandana Rai

Human Molecular Genetics Laboratory, Department of Biotechnology, VBS Purvanchal University, Jaunpur-222003, India

OR (95%CI),p

T vs. C : OR=1.05 (0.99-1.11), 0.09

Association= No

Stages of Ovarian Cancer

healthy ovaries   early-stage cancer   late-stage cancer

https://www.everydayhealth.com/ovarian-cancer/stages/

Prostate Cancer (PCa)

(Global incidence-1276106; Indian incidence-25696)

Symptoms of Prostate cancer-

- Frequent urination
- Weak or interrupted urine flow or the need to strain to empty the bladder
- Blood in urine
- Blood in the seminal fluid
- The urge to urinate frequently at night
- Pain or burn during urination
- Discomfort or pain when sitting, caused by an enlarged prostate

several factors that might affect a man's risk of getting prostate cancer-

Age (the chance of having prostate cancer rises rapidly after age 50. About 6 in 10 cases of prostate cancer are found in men older than 65)

- Family history
- Genetic factors (BRCA2, COMT etc)
- race and ethnicity Lifestyle
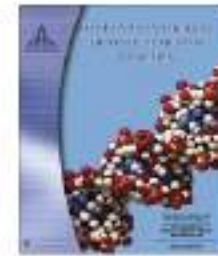- Dietary habits (Obesity, smoking, red meat, high fat foods),
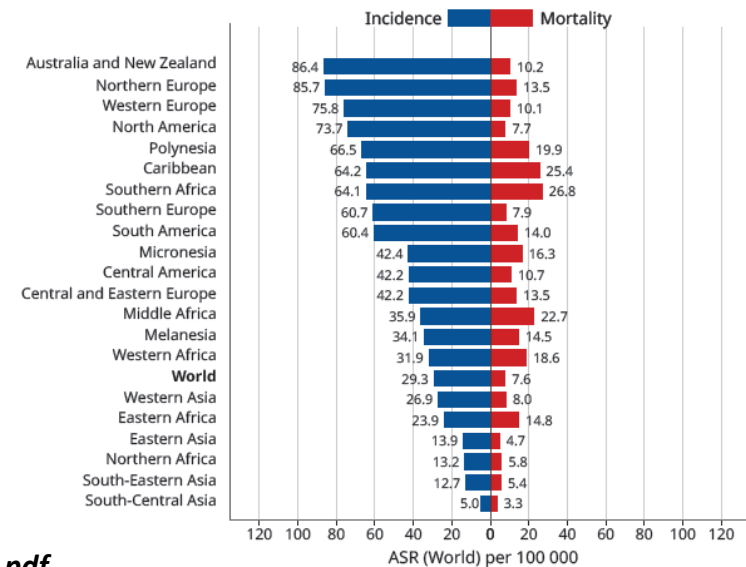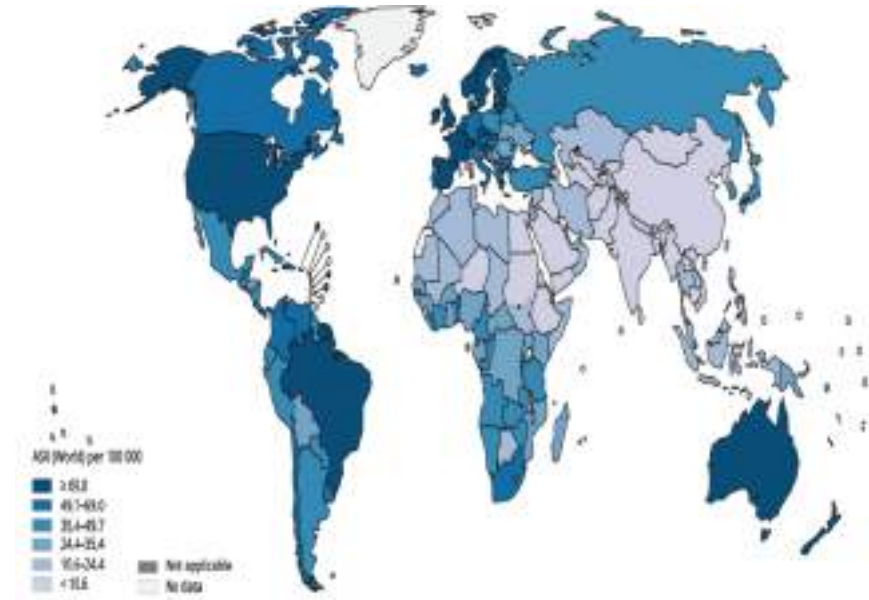
https://gco.iarc.fr/today/data/factsheets/populations/356-india-fact-sheets.pdf

**Incidence and mortality rate of PCa**

REVIEW

Role of *MTHFR* A1298C gene polymorphism in the etiology of prostate cancer: A systematic review and updated meta-analysis

CrossMark

Upendra Yadav, Pradeep Kumar, Vandana Rai *

Human Molecular Genetics Laboratory, Department of Biotechnology, VBS Purvanchal University, Jaunpur 222 003, UP, India

OR (95%CI),p
C vs. A : OR=1.01(0.91-1.13),0.73
Association= No

https://www.pcf.org/about-prostate-cancer/diagnosis-staging-prostate-
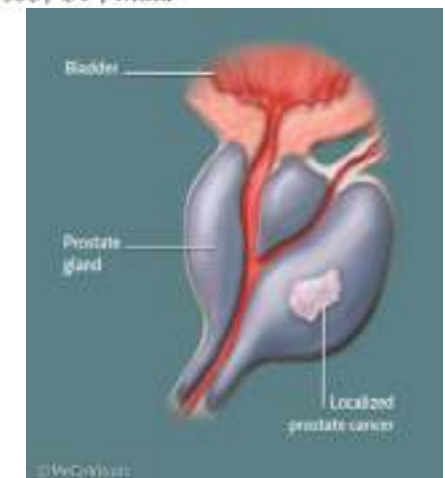
Folate deficiency and Cancer risk

Folate maintains genomic stability by regulating DNA biosynthesis, repair and methylation.

5,10-methylenetetrahydrofolate (5,10-methylene THF) is involved in synthesis of thymidine monophosphate (TMP)as methyl donor.

5,10-formyltetrahydrofolate (5,10-formyl THF) is involved in the production of both adenosine and guanosine (purine). Folate deficiency/MTHFR poymorphism impacts on DNA synthesis and repair by inhibiting production of thymidine, adenosine and guanosine.

Defective DNA repair is linked to human cancer development.

Folate deficiency may induce both gene-specific DNA hypermethylation and global DNA hypomethylation by its DNA-damaging effect.

Global and gene-specific DNA hypomethylation and site-specific hypermethylation are common features in tumorigenesis.

Duthie SJ. J Inherit Metab Dis 2011;34:101–9.
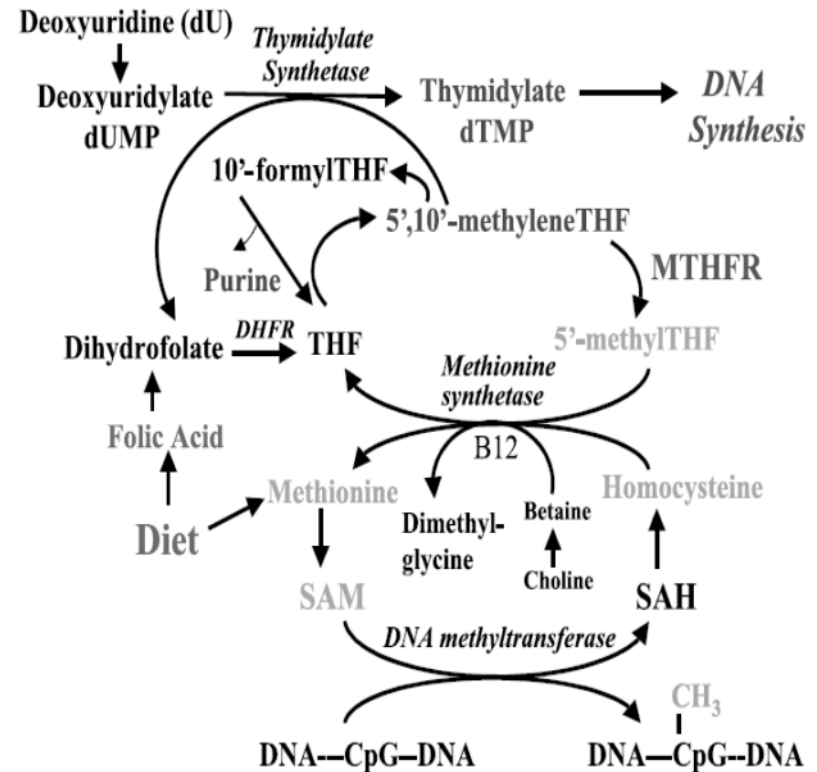
Folate deficiency and Cancer risk
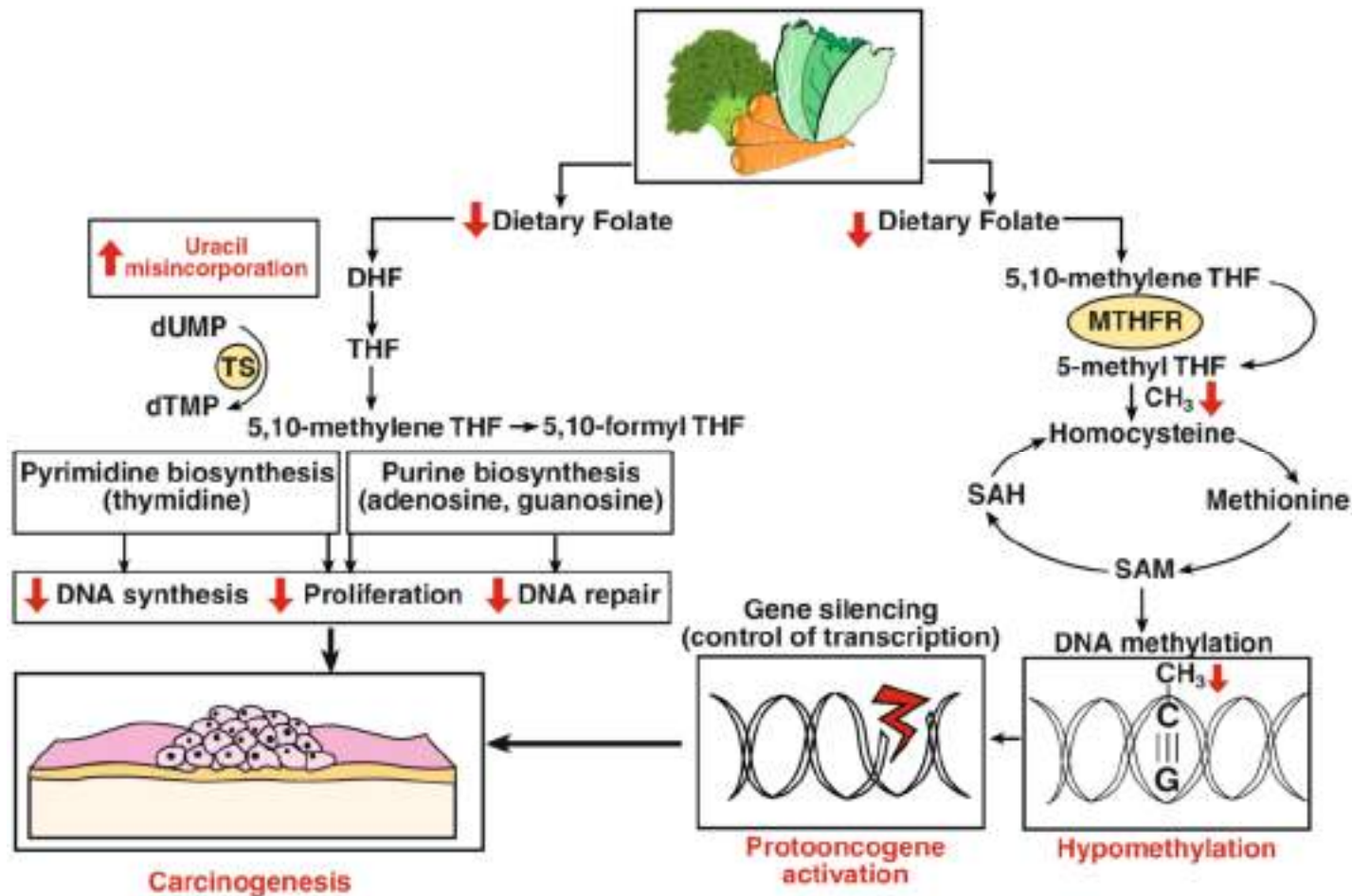
Folate and one-carbon metabolism: regulation of DNA synthesis, repair and methylation. A simplified scheme describing how dietary and cellular folates mediate normal DNA synthesis, repair and methylation and how folate depletion impacts on these processes. DHF dihydrofolate, THF tetrahydrofolate, 5,10-methylene THF 5,10-methylenetetrahydrofolate, 5,10-formyl THF 5,10-formyltetrahydrofolate, 5-methyl THF 5-methyltetrahydrofolate, SAM s-adenosylmethionine, SAH sadenosylhomocysteine, MTHFR methylenetetrahydrofolate reductase, dUMP deoxyuridine monophosphate, TMP thymidine monophosphate, TS thymidylate synthase

Duthie SJ. J Inherit Metab Dis 2011;34:101 –9.