Cancer Susceptibility

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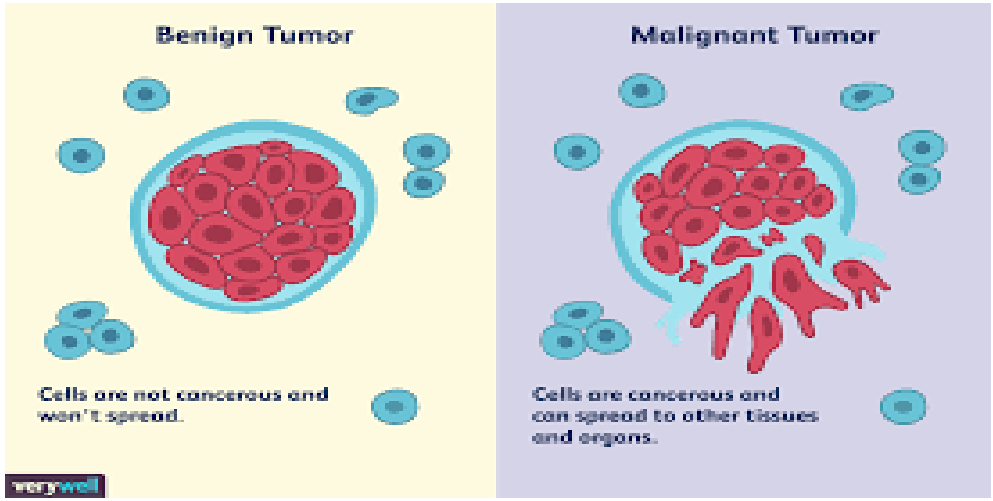
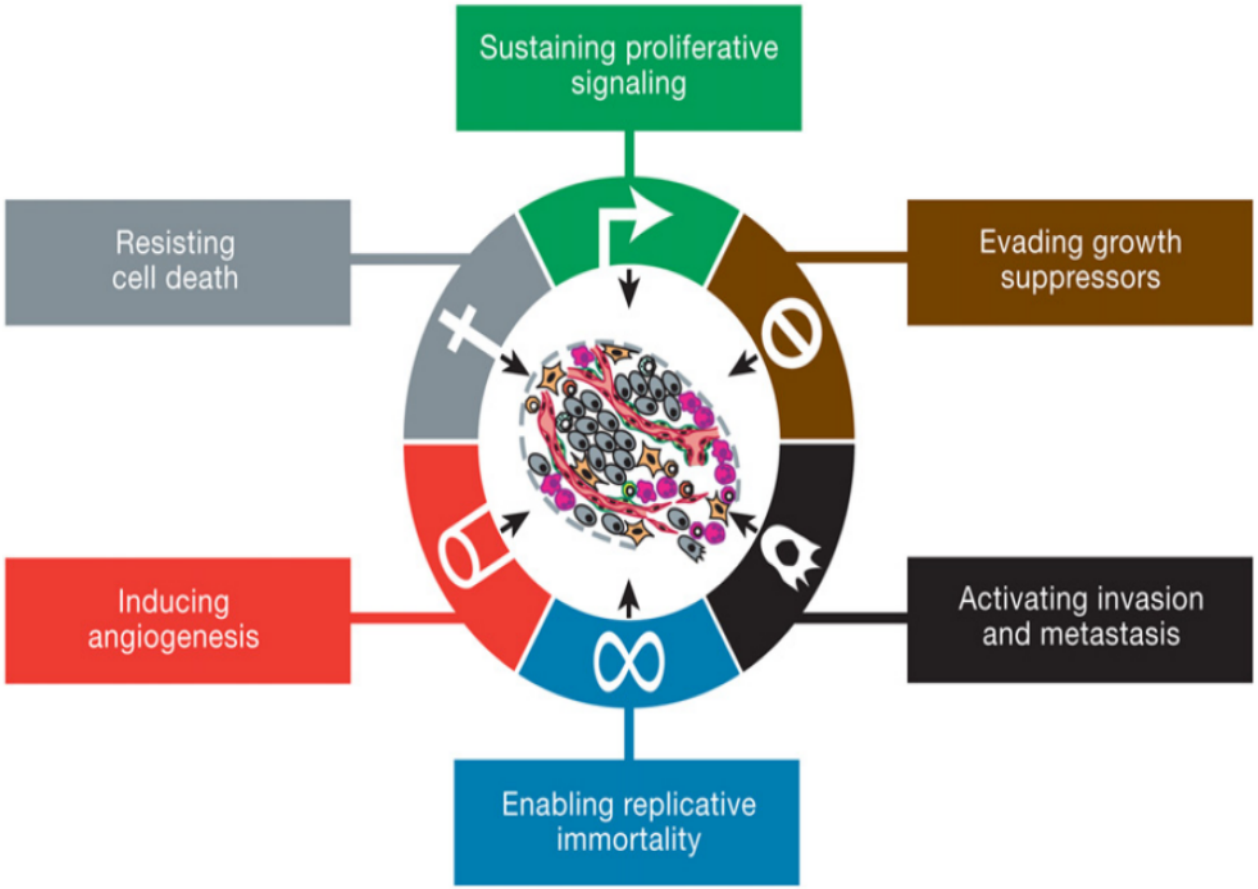
Cancer

- 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.



Cancer Research UK
http://info.cancerresearchuk.org/cancerstats/incidence/?a=5441

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

Hanahan and Weinberg, 2011, *Cell* ***144:646–674.***

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

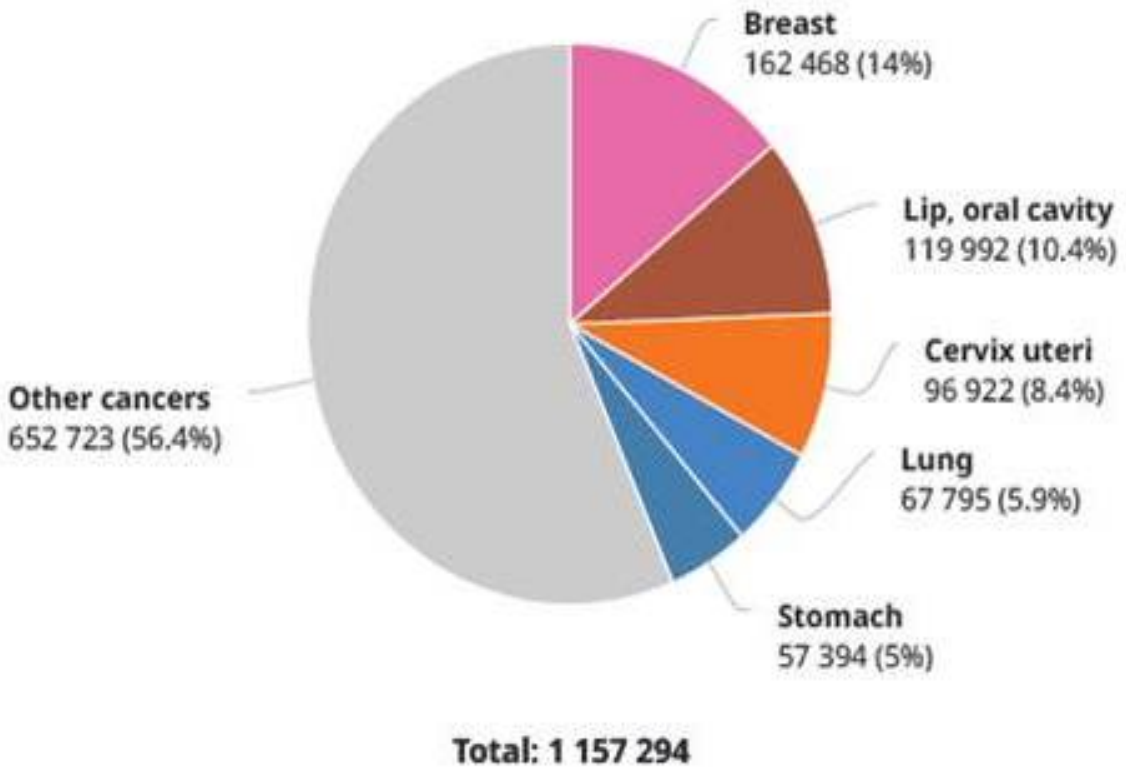
Male				Female		
Prostate	174,650	20%		Breast	268,600	30%
Lung & bronchus	116,440	13%		Lung & bronchus	111,710	13%
Colon & rectum	78,500	9%		Colon & rectum	67,100	7%
Urinary bladder	61,700	7%		Uterine corpus	61,880	7%
Melanoma of the skin	57,220	7%		Melanoma of the skin	39,260	5%
Kidney & renal pelvis	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.

India (Globocan 2018)



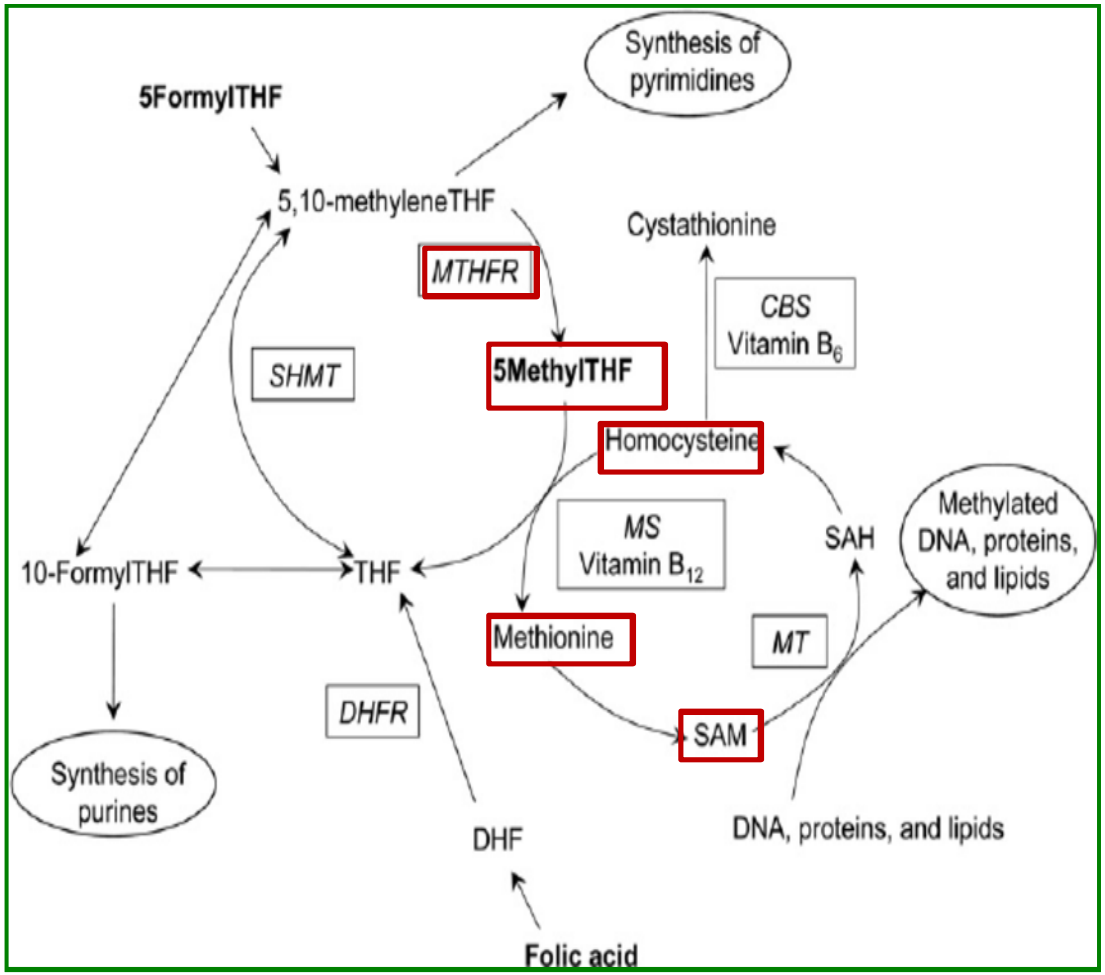
Cancer type	Incidence in 2018	%
Breast cancer	162468	14%
Lip and oral Cavity	119992	10.4%
Cervix uteri	67795	5.9%
Stomach	57394	5%
others	652723	56.4%
Total	1,157294	

Number of new cases in 2018 in both sexes

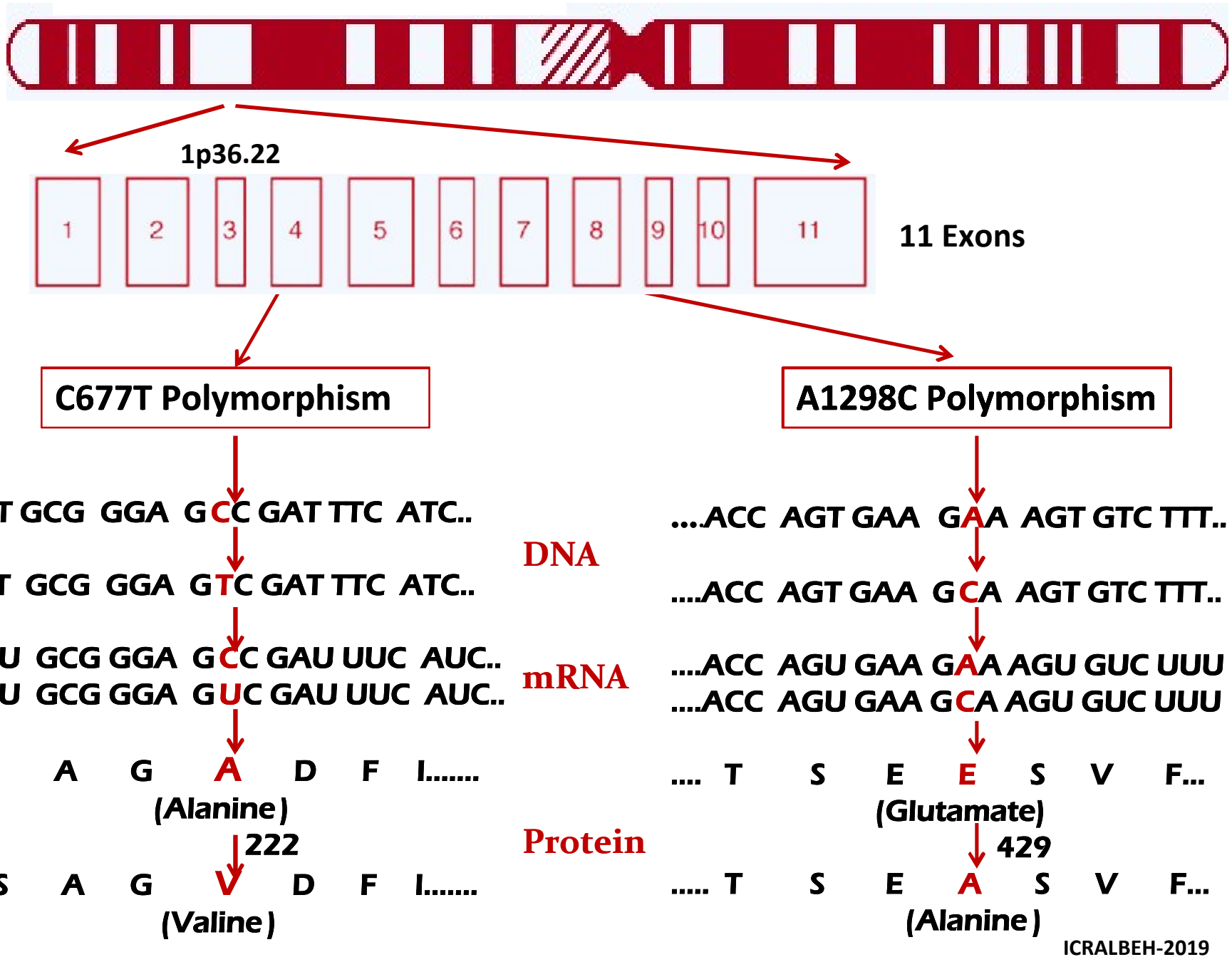
MethylenetetrahydrofolateReductase (MTHFR)

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.**



Hobbs et al ., Am. J. Hum. Genet. 67:623–630, 2000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1
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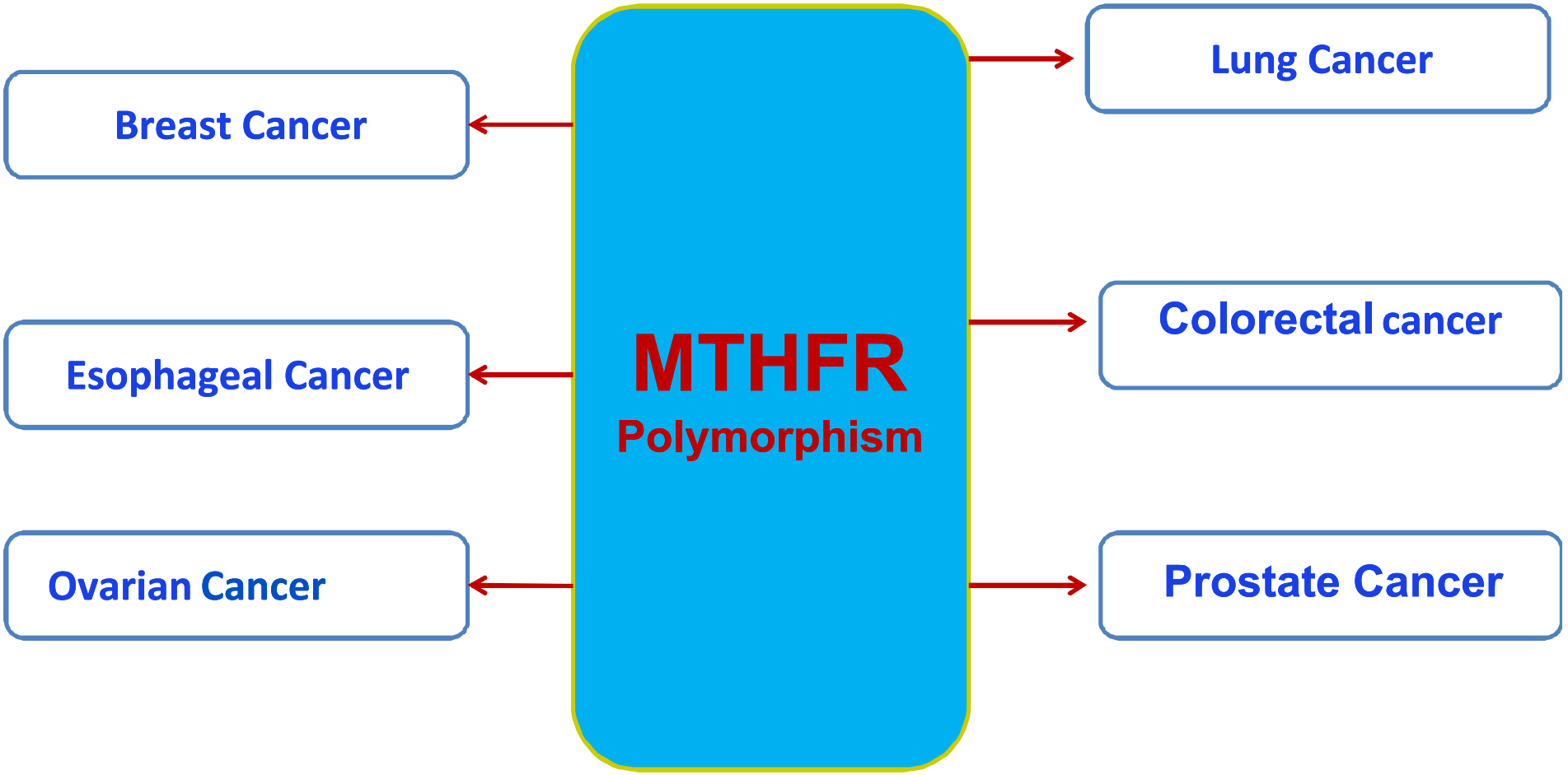
11 Exons
C677T Polymorphism
A1298C Polymorphism
• TCT GCG GGA GCC GAT TTC ATC..
. TCT GCG GGA GTC GAT TTC ATC..
. UCU GCG GGA GCC GAU UUC AUC..
. UCU GCG GGA GUC GAU UUC AUC..
.. S A G A D F I.....
(Alanine)
222
.. S A G V D F I.....
(Valine)
DNA
mRNA
Protein
....ACC AGT GAA GAA AGT GTC TTT..
....ACC AGT GAA GCA AGT GTC TTT..
....ACC AGU GAA GAA AGU GUC UUU
....ACC AGU GAA GCA AGU GUC UUU
.... 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

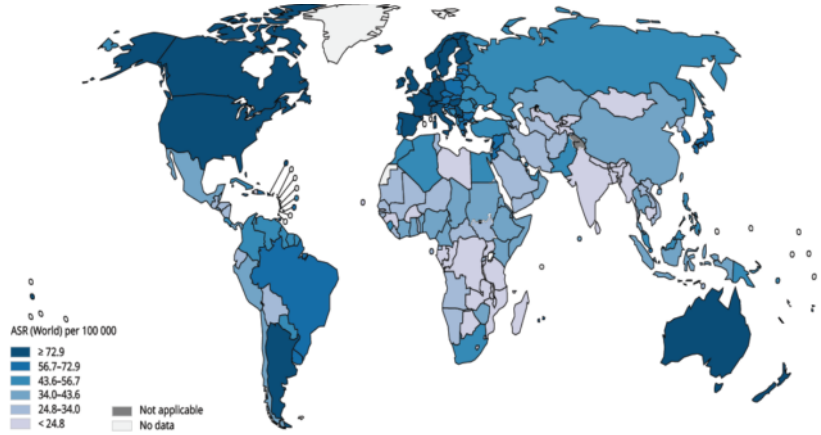
(Global incidence-20,88,849; Indian incidence-162468)

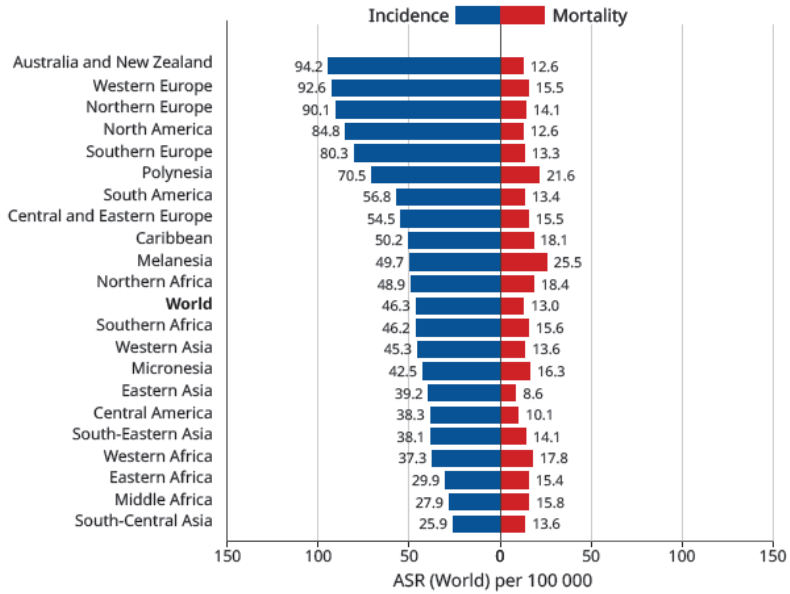
Symptoms:

- 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

MTHFR and Breast Cancer

DOI:http://dx.doi.org/10.7314/APJCP.2014.15.14.5853
The C677T MTHFR Polymorphism as a Risk Factor for 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

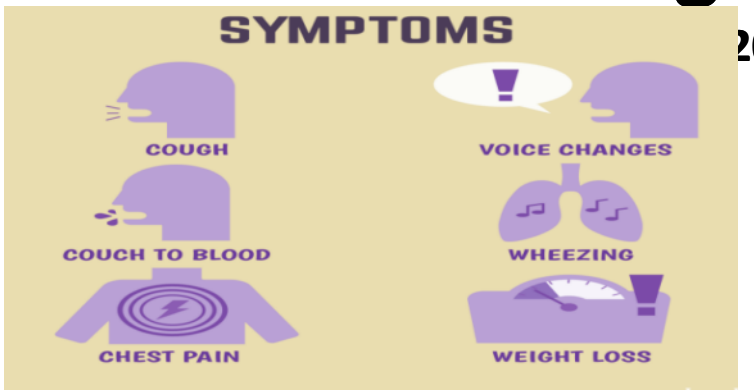
Methylenetetrahydrofolate reductase gene C677T polymorphism and breast cancer risk: Evidence for genetic susceptibility

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)



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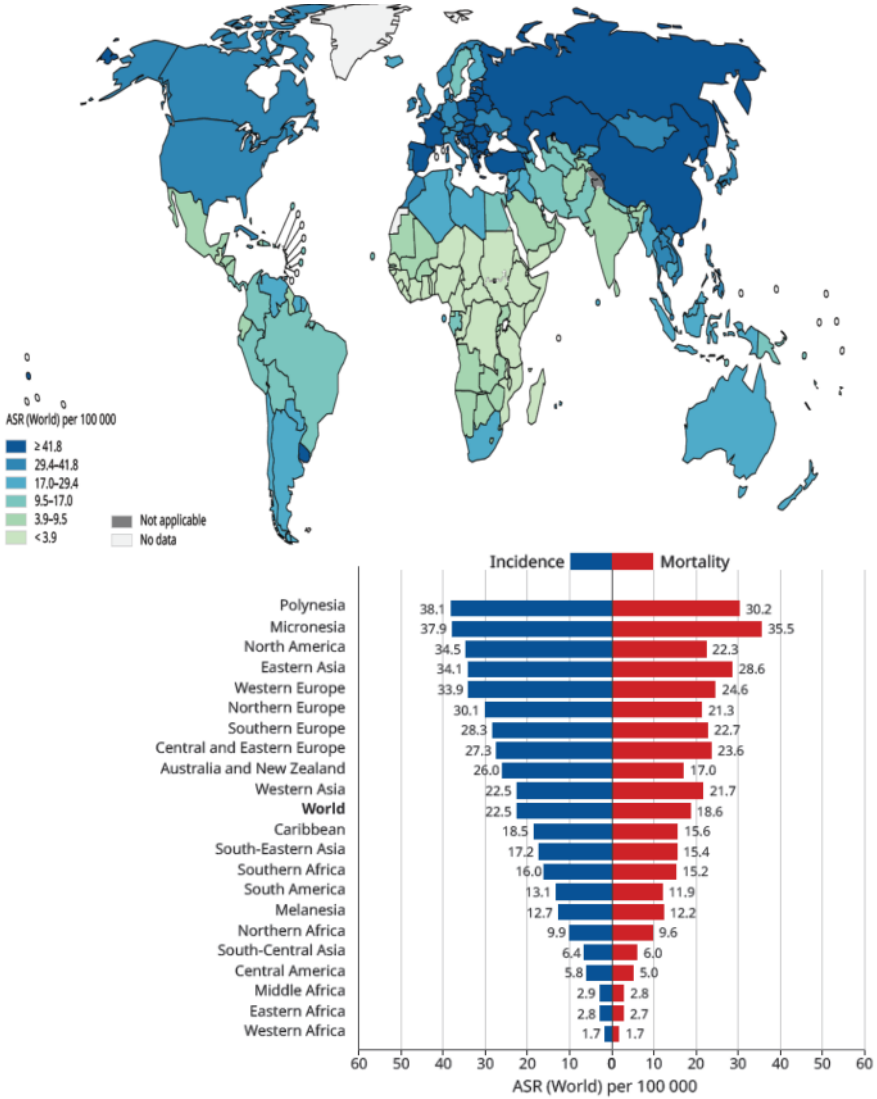


Incidence and mortality rate of lung cancer in 2018

MTHFR and Lung Cancer

DOI:http://dx.doi.org/10.7314/APJCP.2014.15.21.9259
MTHFR C677T Polymorphism as Risk Factor for Lung Cancer in Asians

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:

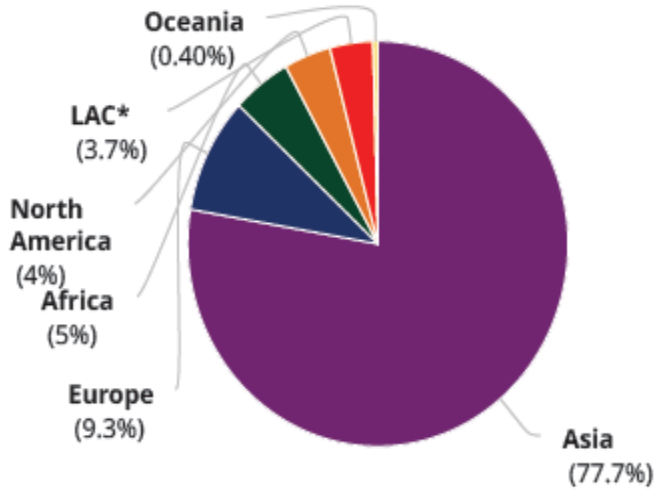
Alcohol consumption,

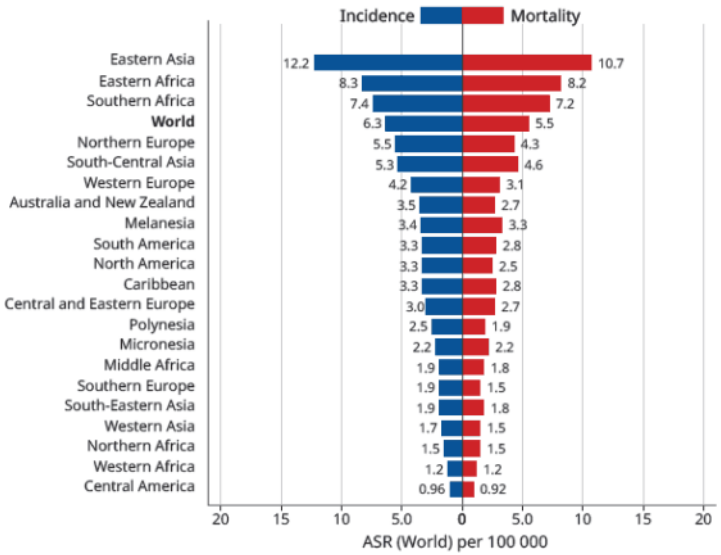
smoking,

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

The Egyptian Journal of Medical Human Genetics 19 (2018) 273–284

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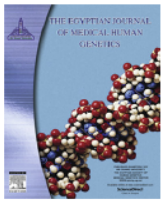
Contents lists available at ScienceDirect

The Egyptian Journal of Medical Human Genetics

journal homepage: www.sciencedirect.com



Review

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

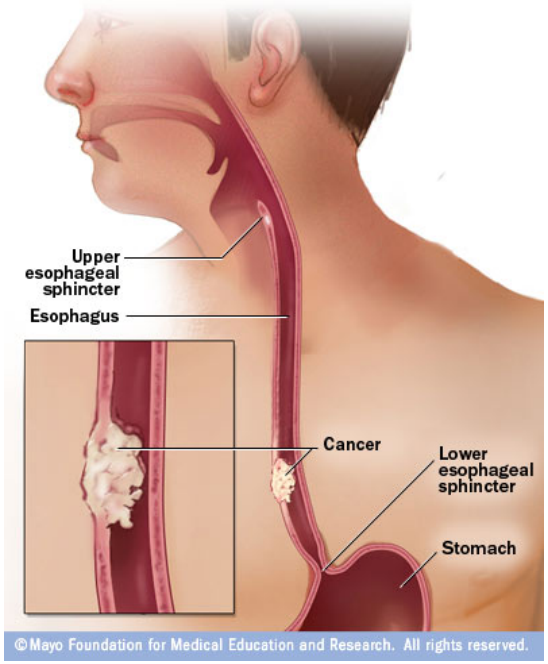
Pradeep Kumar, Vandana Rai *

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-

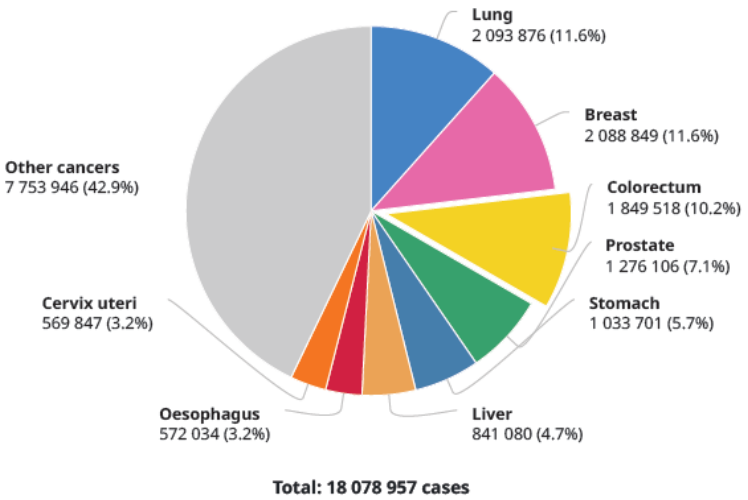
Worsening constipation

blood in stool

decrease in stool caliber (thickness)

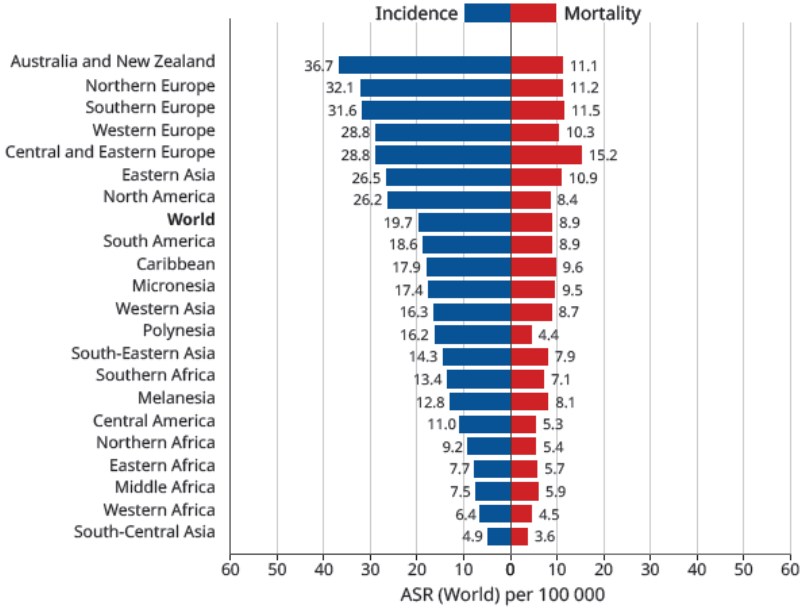
loss of appetite

loss of weight and nausea or vomiting.



Total: 18 078 957 cases

New CRC cases in 2018



Incidence and mortality rate of CRC in 2018

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

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

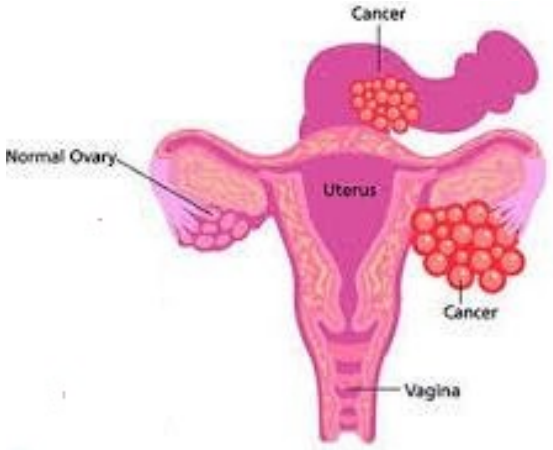
Ovary Cancer

(Global incidence-295414; India-36170)

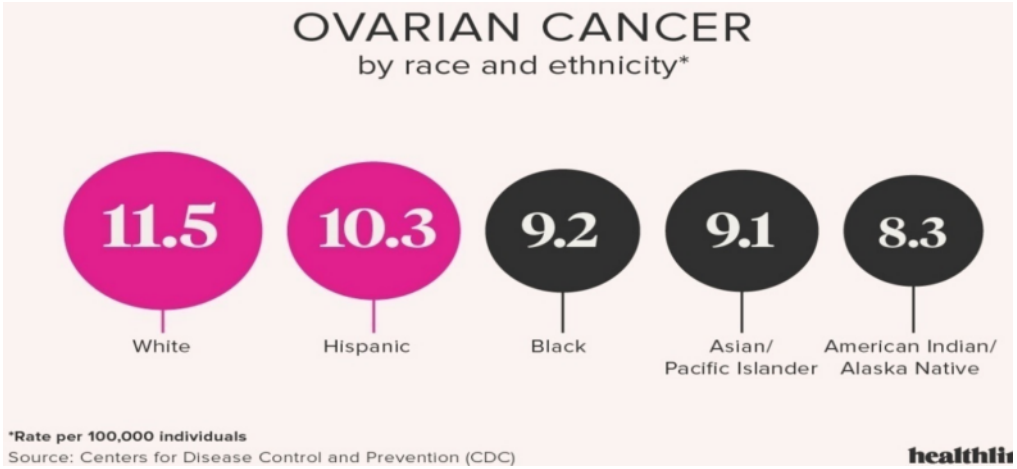
Tumor marker	Ovarian neoplasm
CA-125	Epithelial ovarian cancer
CEA	Mucinous ovarian cancer
HCG	Embryonal carcinoma Choriocarcinoma
Inhibin A or inhibin B	Granulosa cell tumor
Lactate dehydrogenase	Dysgerminoma
α-Fetoprotein	Endodermal sinus tumor Embryonal carcinoma

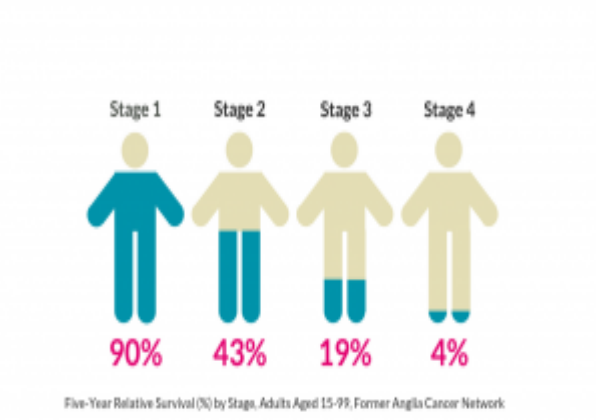
Abbreviations: CEA, carcinoembryonic antigen; HCG, human chorionic gonadotropin.

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



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





Journal of
Health & Medical Informatics

Rai, J Health Med Informat 2016, 7:3
http://dx.doi.org/10.4172/2157-7420.1000226

Review Article Open Access

Methylenetetrahydrofolate Reductase Gene C677T Polymorphism and Its Association with Ovary Cancer

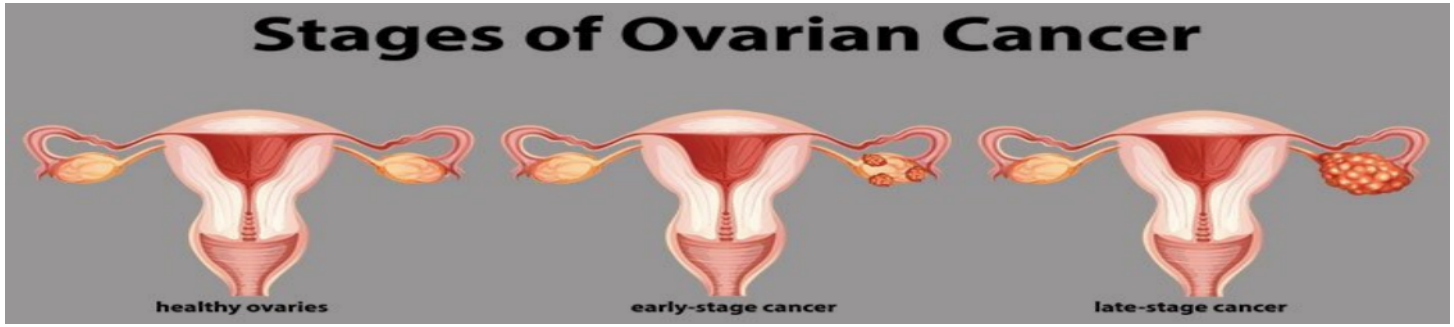
Vandana Rai

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



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

Prostate Cancer (PCa)

(Global incidence-1276106; Indian incidence-25696)

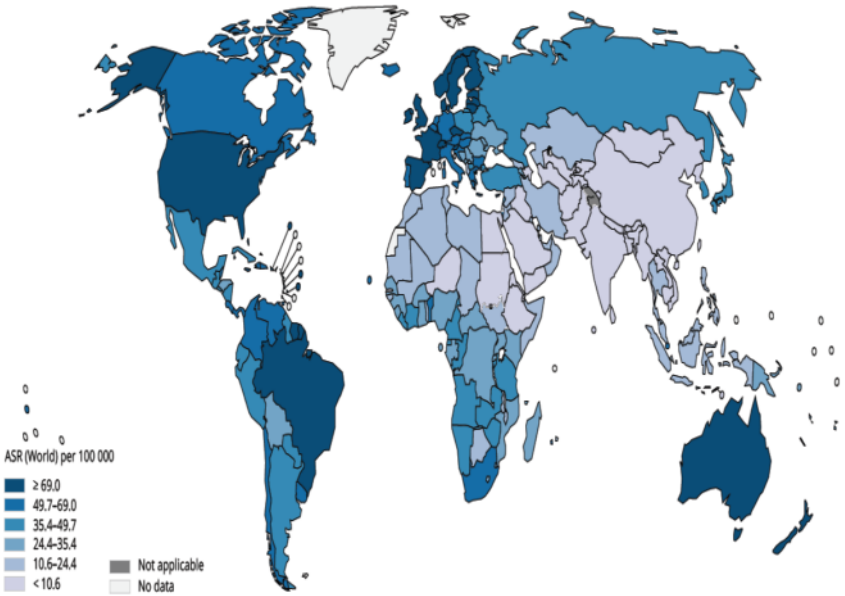
Symptoms of Prostate cancer-

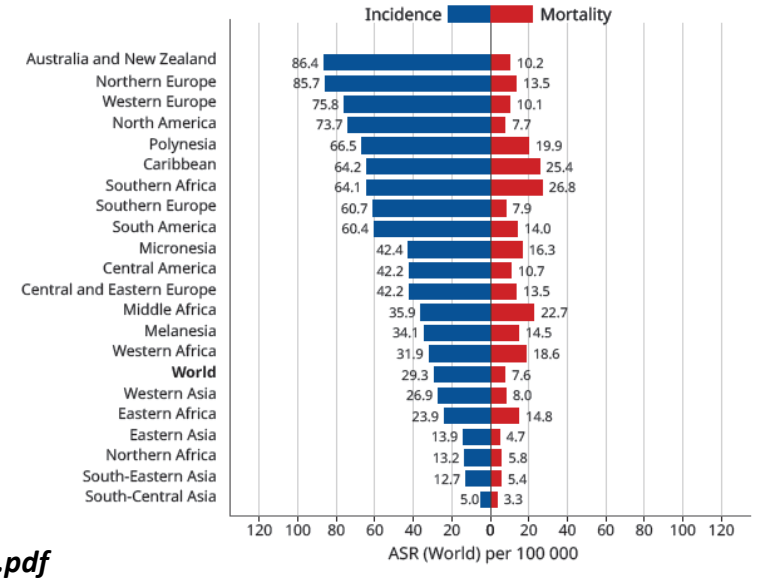
- Frequent urination
- Weak or interrupted urine flow or the need to strain to empty the bladder
- Blood in urine
- Blood in the seminal fluid
- The urge to urinate frequently at night
- Pain or burn during urination
- Discomfort or pain when sitting, caused by an enlarged prostate

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),





Incidence and mortality rate of PCa

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

The Egyptian Journal of Medical Human Genetics (2016) 17, 141–148

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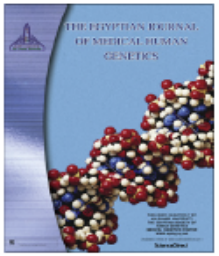


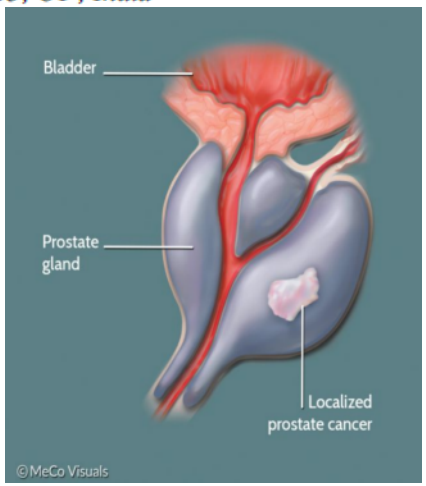
REVIEW

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

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.

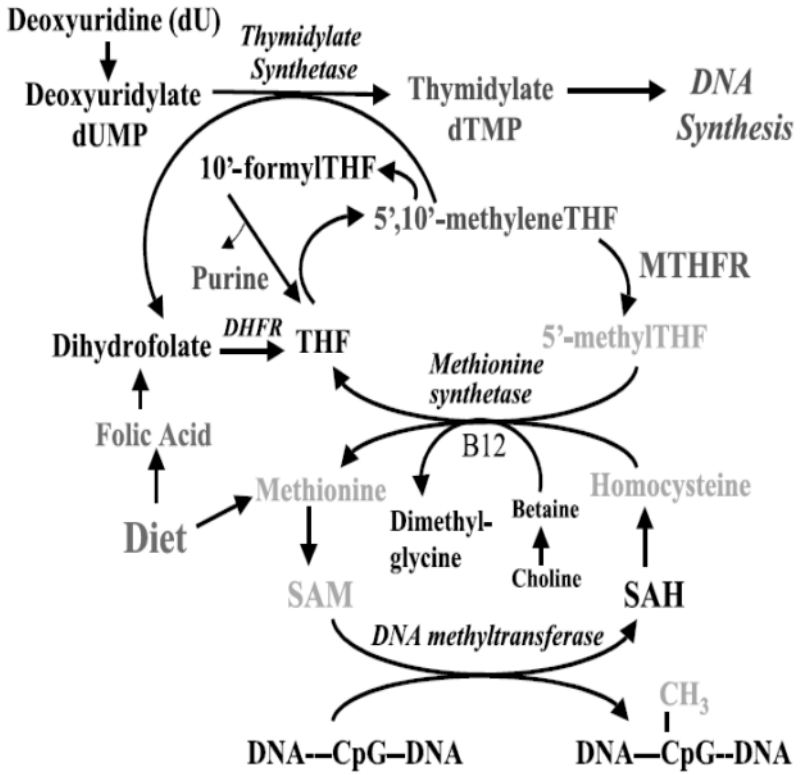
5,10-methylenetetrahydrofolate (5,10-methylene THF) is involved in synthesis of thymidine monophosphate (TMP)as methyl donor.

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.

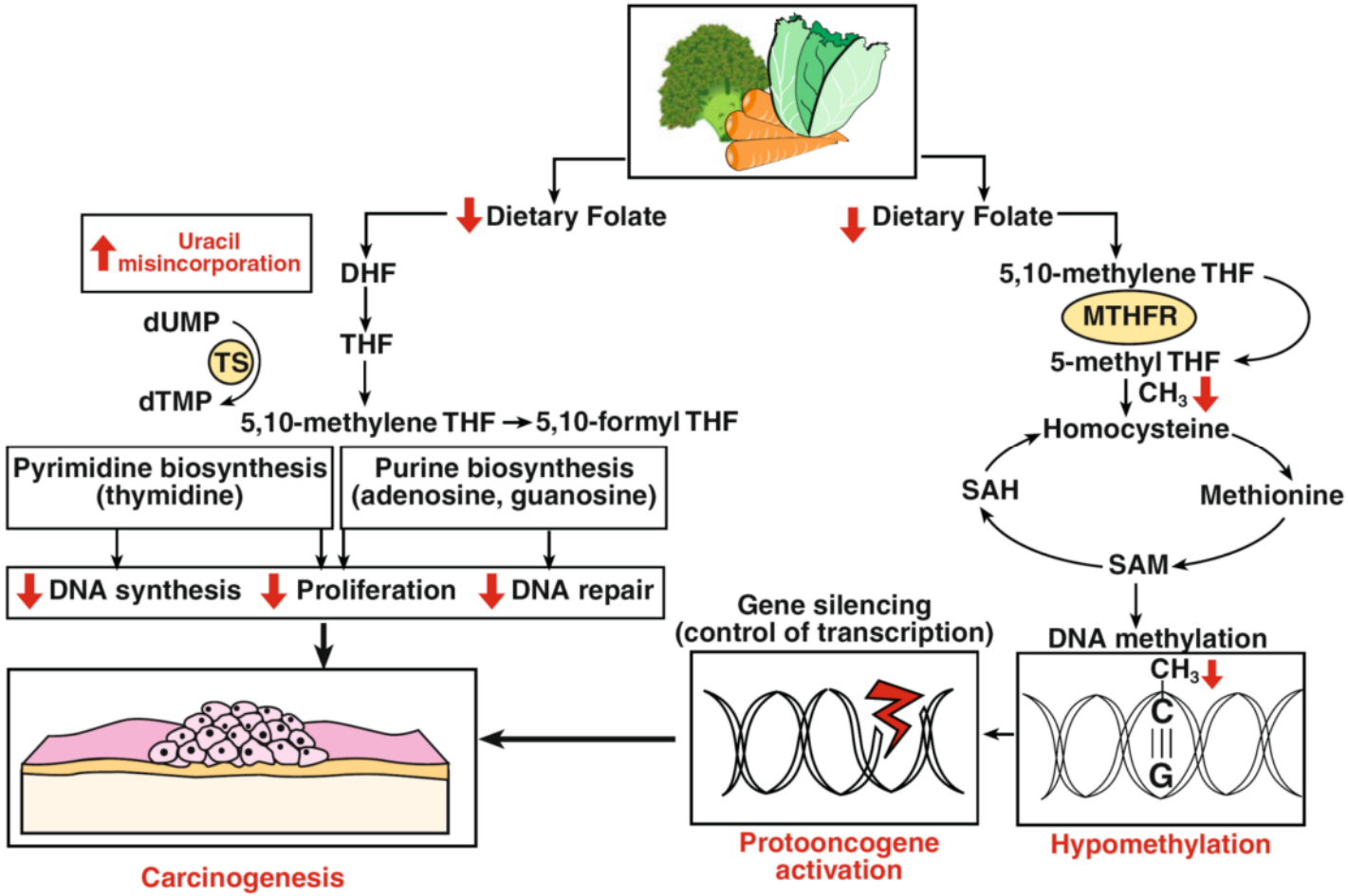
Folate deficiency may induce both gene-specific DNA hypermethylation and global DNA hypomethylation by its DNA-damaging effect.

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.