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Cancer Risk Genes growing from few to many: Are we aware?

Cancer is a group of disorders that are characterized by uncontrolled cell growth beyond their usual boundaries. Other terms used for cancer are malignant tumours and neoplasms. Cancer can affect any part of the human body and can then invade adjoining parts of the body and spread to other organs, called metastases. Metastases are a major cause of death from cancer. Cancer is the second leading cause of deaths globally and according to World Health Organization (WHO), 9.6 million people died of cancer in 2018 of which 70% were from middle and low-income countries. The leading causes of deaths due to cancer worldwide were highest for lung cancer, followed by colorectal cancer, stomach cancer, liver cancer and breast cancer. WHO reported that cancer mortality in Nepal is higher in females as compare to males. Based on hospitals data approximately 8,000-10,000 new cases of cancer are identified every year in Nepal. The growth rate of cancer will have increased from 2013 to 2020.[1,2]

Risk factors

Cancer development is a series of events over a period of many years, during which originally healthy genetic cell material is damaged and the cells change through a number of intermediate stages of the body into tissue independent of the body's regulatory systems. These changes are the result of the interaction between a person's genetic factors and external agents including: Physical carcinogens, such as ultraviolet and ionizing radiation, Chemical carcinogens, such as asbestos, components of tobacco smoke, aflatoxin, and arsenic, and biological carcinogens, such as infections from certain viruses, bacteria, or parasites. Majority of cancer cases the specific cause of the disease cannot be identified. Cancers are a diverse group of diseases, and their causes, progression, symptoms and treatment can differ a great deal from each other. Cancer risk factors include exposure to chemicals or other substances, as well as certain behaviors. They also include things people cannot control, like age and family history. Human factors related to behavior and living habitat are relevant in the development of most cancers. Cancer risk factors can be roughly divided into the following categories:

- Internal factors, such as age, sex, metabolism of substances foreign to the body, inherited genetic defects and non-inherited gene disorders, as well as the type of skin.
- Lifestyle related factors, e.g. tobacco, alcohol, nutrition, hormones, exercise and weight control.
- Occupational exposures, e.g. many chemicals, radioactive materials and asbestos.
- Environmental exposure, e.g. radon and UV radiation, as well as small particles.

Between 30–50% of cancers can currently be prevented by avoiding risk factors and implementing existing evidence-based prevention strategies. Limiting exposure to avoidable risk factors such as alcohol, smoking, cancer causing chemical, radiation and substances, diet, obesity, genetic disease and mutation, infection may lower risk of developing cancers.[3]

Cancer risk Genes

Cancer is a genetic disease and caused by certain changes to genes that control the cells function, especially in cell growth and division. Genetic changes that promote cancer can be inherited from parents if the changes are present in germ cells or Cancer-causing genetic changes can also be acquired during one's lifetime, as the result of errors that occur as cells divide or from exposure to carcinogenic substances that damage DNA, such as certain chemicals in tobacco smoke, and radiation, such as ultraviolet rays from the sun. Genetic changes that occur after conception are called somatic changes. Of the 30,000 or so genes that are currently thought to exist in the human genome, there is a small subset that seems to be particularly important in the prevention, development, and progression of cancer. Genes that promotes cancer are called oncogene and genes that inhibit cancer are called tumor suppressor gene. Next Generation Sequencing (NGS) and Genome-wide Association Studies (GWAS) have highlighted many commonalities in genetic risk and overlap in key pathways across cancer types. Some of the most prominent genes include *MYC, TERTBCL2, BCR,*

AKT, ABL, RAF, REL, HNF1B etc, all of which are linked to a growing number of cancer types. Tumor suppressor genes are *APC, IL2, JAK, ATM, NF1, BRCA2, NF1, TP53* etc. Next-Generation Sequencing (NGS) for large panels of genes or exomes are increasingly and successfully used in medical management for rare diseases and cancer. [4]

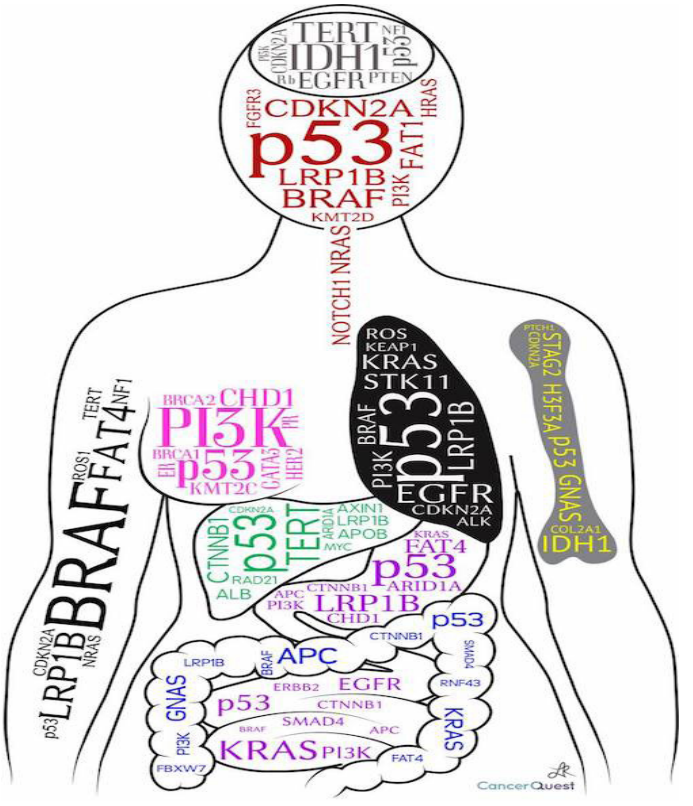

Fig. 1. Cancer related gene.[5]

Table 1. High risk genes with established predictions with surveillance recommendations by American College of Medical Genetics and Genomics (ACMG).[4]

Gene Name	Tumour Types (Germline)	Cancer Syndrome	ACMG Recomm.
APC	colorectal, pancreatic, desmoid, hepatoblastoma, glioma, other CNS	adenomatous polyposis coli; Turcot syndrome	yes
BRCA1	breast, ovarian	hereditary breast/ ovarian cancer	yes
BRCA2	breast, ovarian, pancreatic, leukaemia	hereditary breast/ ovarian cancer	yes
CDH1	gastric	familial gastric carcinoma	no
CDKN2A	melanoma, pancreatic	familial malignant melanoma	no
EPCAM	colorectal	Colorectal cancer, hereditary nonpolyposis, type 8	no
MLH1	colorectal, endometrial, ovarian, central nervous system	hereditary non-polyposis colorectal cancer, Turcot syndrome	yes
MSH2 MSH6	colorectal, endometrial, ovarian	hereditary non-polyposis colorectal cancer	yes
NF1 NF2	meningioma, acoustic neuroma	neuro fibromatosis type 1 and 2	yes
PMS2	colorectal, endometrial, ovarian, medulloblastoma, glioma	hereditary non-polyposis colorectal cancer, Turcot syndrome	yes
SDHB/ SDHD/ SDHAF2/ SDHC	paraganglioma, pheochromocytoma	familial paraganglioma	yes
TGFBR2	colorectal	Hereditary Nonpolyposis Colorectal Cancer type 6	yes
TP53	breast, sarcoma, adrenocortical carcinoma, glioma, multiple other tumour types	Li-Fraumeni syndrome	yes
TSC1 / TSC2	hamartoma, renal cell carcinoma, tuberous sclerosis tuber	Tuberous sclerosis 1	yes
FANCA/ FANCB/ FANCC/	Acute myeloid leukemia, leukaemia	Fanconi anaemia complementation group A, B, C, D, E, F, G, L, respectively	no

Genetic Testing

Genetic tests for mutations that cause cancer syndromes are usually requested and genetic counseling can help to consider the risks, benefits, and limitations of genetic testing. Lab tests called DNA sequencing tests can "read" DNA, NGS and GWAS. By comparing the sequence of DNA in cancer cells with that in normal cells, such as blood or saliva, can identify genetic changes in cancer cells that may be driving the growth of cancer. In NGS, the specific gene panels are chosen to select the panel containing the relevant genes/variants of clinical utility and validity. GWAS is an observational study of a genome-wide set of genetic variants associated with a trait. GWASs typically focus on associations between single-nucleotide polymorphisms (SNPs) and traits like major human diseases.

CONCLUSION

Many cancers are not linked with a specific gene and may involve multiple gene mutations. Evidence suggests that genes interact with their environment. Researchers continue to study how genetic changes affect cancer development and this knowledge has led to improvements in cancer care, including early detection, risk reduction, the use of targeted therapy, and survival. Globally, genetic counseling, genetic testing and gene therapy has been started, however, in contest of Nepal, no genetic laboratory has been well setup both in government and private level. In Nepal, cancer genetic testing like DNA sequencing, NGS and GWAS is urgently needed to be started.

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