

Gene in Multiple Cancers



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Genes are the determinants of individual appearance or phenotype. Several studies reveal the clinical association between genes and cancer. To study the genes and their relationship to cancer is the present focus in clinical oncology. In this specific brief review, the author would like to introduce a group of genes that are associated with multiple cancers.

In carcinogenesis, a complex process has to occur.^{1,2} Briefly, there are two main contributing factors that lead to cancer development. One is genetic and the other is environmental.³⁻⁷ Genes are the determinant of individual appearance or phenotype. Several studies reveal the clinical association between genes and cancer. To study the genes and their relationship to cancer is the present focus in clinical oncology. With advancements in post-genomic bioinformatics technology, many new gene profiling techniques allow medical scientists to measure the expressions of many genes. Also, informatics can help clarify and predict the association between gene disorders and development as well as progression of malignancy.

Studying the relationship between genes and cancer can provide much useful data in clinical oncology. The derived data can be used for diagnosis, therapy and prognosis predictions. Briefly, there are three groups of genes which are classified according to their known relationship to cancer.^{8,9} The first group is the genes with confirmed evidence that they relate to cancer. The second group is the genes with confirmed evidence that they do not relate to cancer. The last group is the genes without clear evidence for their relationship to cancer. The genes which are being focused on by biomedical researchers at present are those in the first group.

In this specific brief review, the author would like to introduce a group of genes that are associated with multiple cancers. It is the case that one gene mutation can result in multiple cancers in a patient.

Multiple cancers: an interesting pathology

Put simply, cancer is the uncontrolled growth of cells that can invade nearby structures as well as migrate to remote organs (metastasis). Due to the invasive nature of cancer, it can result in death. Generally, a patient might develop malignancy if the required genetic and environmental disorders are fulfilled.³ In general, the malignancy in a patient is usually due to a single cancer (with or without metastasis). This means there is only one primary focus of the malignancy that causes the disease in the patient. However, in some uncommon cases, there might be more than one foci in a patient. This is called multiple cancers.

Table 1: Some interesting reports on multiple cancers

Authors	Combination
Capaldo et al. ¹²	Ovarian carcinoid tumor, mucinous cystadenoma of low malignant potential tumor of left ovary, and adenocarcinoma of colon ¹²
Demandante et al. ¹³	Synchronous ureteral/bladder/urethral transitional cell carcinoma and prostatic adenocarcinoma ¹³
Kobayashi et al. ¹⁴	Uterus, stomach, breast cancer and glioblastoma multiforme ¹⁴ , uterus, stomach cancer and glioblastoma ¹⁴
Klochikhin et al. ¹⁵	Neoplasm of the laryngopharynx and stomach ¹⁵
Sielanczyk et al. ¹⁶	Endometrial uterus cancer, breast cancer and thyroid cancer ¹⁶

Multiple cancers is an interesting pathology. Below are some pathological descriptions of multiple cancers:^{10, 11}

- Primary cancers that appear in a patient in different organs at the same time
- Cancer found in both sides of paired organs such as breast and kidney is not considered as a cancer in different organs
- Different kinds of malignancies in the same organ are considered as a cancer in the same organ
- The uterus with adnexa and the lower intestine are each classified as single organs
- There must be histological confirmation of malignant nature
- Metastatic lesions are not considered as a new primary cancer
- The malignancy must not be the result of previous cancer therapy (chemotherapy or radiotherapy)

These criteria are called “*Werthamer criteria*”.¹⁰ Multiple cancers is classified as a rare syndrome that can be seen in less than 1 % of cancerous patients. Some rare combinations are sporadically reported in literature¹²⁻¹⁶ (Table 1). Focusing on the natural history of multiple cancers, Schoenberg¹⁷ analyzed the Connecticut data during 1935-1964 and concluded that “*individuals with one malignant neoplasm have 1.29 times the risk of developing a new independent primary tumor when compared to individuals who never had cancer*”. However, the increased risk seems to be site dependent. According to another newer study by Ray et al.¹⁸, no increased risk could be observed for prostate cancer. Similar findings were also reported for laryngeal cancer.¹⁹ Also, in this work¹⁹, the size and site of the laryngeal tumor was shown to have no relationship to the occurrence of other primary cancers. Patients with multiple cancers usually have a family history of cancers. However, no family history can also be seen.¹⁶

Role of genes in hereditary multiple cancer syndrome

As noted, genetic defects is an important basic requirement for carcinogenesis. For some cancers such as retinoblastoma, there is already copious information on the underlying gene mutations that cause the cancers. For multiple cancers, the genes that have correlation are of

interest. There are several, specific groups of multiple cancers that have strong evidence of genetic inheritance. The so called hereditary multiple cancer syndrome is the name of those disorders.²⁰⁻²² Indeed, one-twentieth of overall cancers have a clear hereditary pattern. Those cancers are proved for passing from one to the next generation. Hence, the role of gene defect can be proven. Well-known hereditary syndromes include hereditary breast and ovarian cancer syndrome, Cowden syndrome and multiple endocrine neoplasia. The details of some important hereditary multiple cancer syndrome will be further discussed.

A. Von Hippel-Lindau disease

Von Hippel-Lindau disease (VHL) is a rare disease that involves many organ systems. The main disorders can be seen in the vascular system. It can be benign or malignant. In benign cases, the abnormalities might be angiomas. In malignant cases, hemangioblastomas can be seen. The malignant hemangioblastomas in VHL are common at retina, brain and spinal cord.²³⁻²⁵ The concomitant primary tumors include adrenal tumor, kidney cancer and pancreas cancer.²³⁻²⁵ Hence, it is a rule to completely investigate for these possible cancers in patients presenting with the VHL.

Focusing on the genetic defect in the VHL, the widely mentioned gene is the VHL gene. Mutations within the VHL gene can be seen in almost all patients with VHL. Generally, the VHL gene is responsible for the production of a specific protein, namely pVHL (213 amino acid residues, molecular weight of 24 to 30 kDa).²⁶ Normally, this derived protein helps inhibit the hypoxia-inducible factor (HIF) via post-translational prolyl hydroxylation with use of a conserved family of Egl-nine enzymes and further targeting HIF for ubiquitin-mediated degradation.²⁶⁻²⁷ Aberration of the protein function is believed to be the starting point of carcinogenesis.²⁶ This is well observed in the case of renal cell carcinoma.^{26, 28, 29}

B. Cowden syndrome

Cowden syndrome (CS) is another rare multiple cancer syndrome whereby its underlying genetic pathology has been proven. The nature of this disease is the

development of multiple tumor-like growths (hamartomas) of the skin and mucous membranes. Sometimes, abnormal growth can also be seen at the gastrointestinal tract or central nervous system. There are also reports on the increased risk of breast, uterus and thyroid cancers.³⁰⁻³³

Focusing on the genetic defect in CS, the widely mentioned gene is PTEN gene.^{34,35} The mutations within PTEN gene can be seen in almost all patients with PTEN. Generally, PTEN is a tumor suppressor gene on 10q23.3 which corresponds to encoding a lipid phosphatase that lies upstream of protein kinase B (Akt).^{35,36} PTEN negatively regulates cell interactions with the extracellular matrix and the aberration of this normal function can result in carcinogenesis.³⁵

C. Li-Fraumeni Syndrome

Li-Fraumeni Syndrome (LFS) is another rare disorder with onset in the young. Increased risk of many cancers is observed in LFS. The problematic cancers include soft tissue sarcomas, breast cancer, leukemia, lung cancer, adrenocortical cancer and brain cancer.³⁷⁻³⁹

Focusing on the genetic defect in CS, the widely mentioned gene is the TP53 gene.^{40,41} The mutations within the TP53 gene can be seen in approximately 50% of the cases and common mutations are missense mutations, located between exon 5 and exon 8, within the DNA-binding domain of TP53.⁴¹ At present, the investigation for TP53 is more widely available. It is recommended for testing in any case with a tumor in the general population, belonging to LFS.⁴¹

D. Lynch syndrome

Lynch syndrome or hereditary non-polyposis colorectal cancer syndrome is another rare genetic disorder presenting with early age onset colorectal cancer, endometrial cancer and other extracolonic malignancies.⁴²⁻⁴⁴ The mutations in DNA mismatch repair genes (MLH1, MSH2, MSH6 or PMS2) have a proven relationship to Lynch syndrome.⁴²⁻⁴⁴ Due to the high incidence of colorectal cancer in the West, attempts to launch the screening investigation for Lynch syndrome have been widely mentioned and have been approved for their cost

effectiveness.⁴⁵ For screening, a combination of various genetic and immunohistochemical tests are used.⁴⁶

E. Muir Torre syndrome

Muir Torre syndrome is a variant of Lynch syndrome. It is strongly related to skin cancers. The genetic disorder is usually within one of the DNA mismatch repair genes and can be seen in up to 70 % of the cases.^{47,48}

F. Turcot syndrome

Turcot syndrome is another variant of Lynch syndrome. It is strongly related to brain cancer (glioblastoma or astrocytoma).^{49,50}

G. Hereditary breast and ovarian cancer syndrome

Hereditary breast and ovarian cancer syndrome is a genetic disorder that has a proven relationship to mutations in the BRCA1 and BRCA2 genes. It is related to the increased risk of many cancers including breast cancer (in both sexes), ovarian cancer and prostate cancer. Also, there are some reports of a risk for pancreatic cancer and melanoma.^{51,52}

Focusing on the risk, an 85% lifetime risk of breast cancer and up to a 46% lifetime risk ovarian cancer are reported.⁵³ Preconception counseling is recommended for this syndrome.⁵⁴

Conclusion

Gene defects is an important underlying pathology in multiple cancers. There is already confirming evidence on the underlying abnormality of some genes in several multiple cancers. Investigation into those problematic genes can be a basic screening tool for early detection and recognition of the possible occurrence of multiple cancers in a cancerous patient. There is no doubt that many primary cancers might be concurrent in a patient but only one cancer might be initially detected. If it is affordable, screening should be performed in any cancerous patient as early as possible. Early diagnosis is the core concept in any cancer therapy, whether multiple or not.⁵⁵

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