Microsatellites are base sequences in the genome, also known as short and sequential repeat sequences. These sequences are in connection with more than one gene. Microsatellites, which are widely distributed in the genome, are codominant in character and highly polymorphic. They are generally one-six base pairs long repetitive sequences, and their frequency in the human genome is 3%. Microsatellite-originated nucleotide repeats occurring in deoxyribonucleic acid (DNA) are indeed mutations. These mutations make humans and even all living things genetically diverse and among each other. Microsatellites are repeats found in both coding (protein-encoding) and non-coding (non-protein-coding) regions of DNA.

Due to the repetitive nature of microsatellites, the DNA polymerase enzyme may make a reading error during the DNA replication stage. Failure to correct these reading errors in DNA also causes frameshift mutations and protein mutations. These mutations usually occur in parts of microsatellite repeats that contain gene regions such as Transforming growth factor-beta receptor 2 (TGFβ-R2), insulin-like growth factor 2 (IGF-2), E2F transcription factor 4 (E2F4), and Bcl-2-associated X protein (Bax) protein. These errors in DNA can normally be repaired by a system called mismatch repair (MMR), and in some cases, this repair mechanism may also fail.

Microsatellite instability (MSI) is a condition that develops due to underlying defects in the MMR genes. In humans, the MMR system consists of the proteins mutL homolog 1 (MLH1), mutL homolog 3 (MLH3), mutS homolog 2 (MSH2), mutS homolog 3 (MSH3), MutS homolog 6 (MSH6), post-mortem submerged interval (PMSI), and PMS 1 homolog 2 (PMS2). This system is responsible for recognizing abnormalities that may arise from physical and chemical errors that may occur during DNA replication. MSI is usually caused by the inactivation of the MMR gene due to mutations in one of the MMR genes. MSI is divided into three classes as low unstable (MSI-L), high unstable (MSI-H), and stable (MSS). Although MSI incidence in cancers such as uterus, stomach, ovarian, liver, brain, and skin is different, nearly 90%
of colon cancer patients with Lynch syndrome (LS) are seen as mutS Homologs (MSH). This is because mutations occur in more than two MMR proteins during replication. Many studies have shown that MSI plays an important role in the pathogenesis and formation mechanism of malignant tumors, and is closely related to disease progression and predicted recovery.

CANCER

Cancer has been a common health problem in humans and animals throughout history. The earliest known records regarding cancer show 3000 years BC. It has been reported that the term cancer derives from the Latin words “canker” or “carcinos”, which means crab. Hippocrates used this term at that time because he likened the swollen veins surrounding the tumor to a crab. In the later periods, the Greek doctor Galen (130-200 AD) used the term “oncos”, which was also used to mean swelling and was instrumental in the formation of the current term oncology. In brief, cancer is a disease characterized by uncontrolled division, proliferation, and accumulation in cells of a living organism. It can affect only one organ, as well as spread to many organs. Each person’s DNA being different is one of the most important factors in cancer formation. Since biological conditions such as the division and reproduction of our cells occur under the influence of genes, it can be said that cancer is related to genes. Genes are structures that are packaged on chromosomes. Physical and chemical mutations in genes can directly affect the cell’s function. There are repair mechanisms in DNA to prevent permanent damage due to these changes in genes. However, these mechanisms may not always function properly. In some cases, changes occur in the gene regions in the parts where the microsatellite repeats occur in the DNA, and the MMR mechanism may not work correctly. In these cases, MSI occurs. MSI has now been associated with many types of cancer.

GENETIC INSTABILITY IN CANCER CELLS

Deficiency in the MMR system causes MSI, and it frequently occurs in certain tumor types. MSI means that despite fluctuations in the length of microsatellite sequences, the genes of the MMR system are not working correctly. MSI is seen in 90% of tumor cases occurring in patients with hereditary LS and 10-15% of sporadic type colorectal cancers (CRCs). Gene inactivation in the MMR repair mechanism activates tumor formation in many different systems. However, it has been reported that the clinical features of tumors with MSI, especially in the gastrointestinal system, show different clinical findings compared to other tumor types. Cancers due to MSI are extremely common in humans. These types of cancer are associated with mutations in genes encoding important proteins of the MMR system. LS is one of the most common susceptibilities in cancer. In LS, different types of tumor tissues (stomach, colorectal, endometrium, breast, kidney, pancreas, lymphoma, etc.) can occur in people before the age of 50. A more severe variant of LS has been reported and called constitutional mismatch repair deficiency (CMMRD) syndrome. In people with this syndrome, one of the genes that form the MMR system undergoes a single allelic germline mutation and causes the formation of tumor tissues that can be seen especially at a young age, even in childhood. Cancers that may occur due to CMMRD syndrome can be listed as lymphoma, leukemia, colon cancer, and certain brain tumors. Cancers associated with MSI can also occur sporadically without a familial factor. Some analyzes and algorithms have been developed for the diagnosis and treatment of CMMRD and LS.

In particular, an algorithm known as the Bethesda system has been developed to be used in the diagnosis, treatment, and disease course of tumors caused by LS, and thus it is possible to predict the tumor phenotype. According to this system, if instability in MSI marker genes is detected in two or more sequences, it is called MSI-H tumor, and if it is detected in only one sequence, it is called MSI-L. If there is no instability in any of the sequences, it is interpreted as the central nervous system (the phenotype of the tumor is stable). In this algorithm, the age limit is set as 50 years. In tumors that develop in people under this age group, the presence of MSI is primarily investigated. According to the microsatellite phenotype and the tissue expression of the proteins involved in the MMR mechanism, it is decided whether the tumor is a tumor of LS or not.

In summary, MSI is frequently encountered in LS origin cancers. Especially in the young patient group, the first suspicion is the presence of MSI. Discovering the existence of MSI has been one of the most important achievements of recent years in the process of cancer diagnosis and treatment.

LYNCH SYNDROME AND MICROSATELLITE INSTABILITY

Lynch syndrome was first described in CRC patients, and its form in these patients was named as...
"hereditary non-polyposis colorectal cancer (HNPCC)"). LS is a genetic condition that shows autosomal dominant inheritance caused by the type of germline mutation that occurs in genes belonging to the DNA MMR system. Being autosomal dominant means that it is affected by mutations that occur outside the chromosomes that determine the sex. However, it is wrong that every individual who has LS findings on the chromosomes taken from the mother and father will have the risk of getting this syndrome.\[^35\] When CRC was examined, 3-5% of tumor cases have been associated with germ mutations that occur in the MMR genes. LS is one of the important reasons for the serious increase in CRC cases. In thirty years, since the discovery of MSI and the acceptance of germline mutations as an etiological cause in LS, early diagnosis and risk reduction strategies have been developed in cancers associated with LS. In recent years, positive changes have been observed in treatments with immune checkpoint inhibitors for cancers associated with LS.\[^35,36\] In addition, the more frequent use of new generation sequencing technologies provides the opportunity to diagnose LS in the early period.

Four practical applications have been reported for LS:\[^35\]

- Testing polymerase chain reaction (PCR)-based MSI of MMR proteins in all colorectal and endometrial cancers is an important screening method for LS.
- Next-generation sequencing is extremely important in detecting germline mutations directly for MSI screening.
- Treatment with anti-programmed cell death protein-1 (PD-1) monoclonal antibodies for advanced LS-associated cancers has been reported to provide a good rate of disease control even in highly resistant tumors.
- It has been reported that 600 mg of aspirin consumption per day reduces the risk of LS-associated CRC by 50% with use for two years or more.
- Individuals with LS can reduce the risk of getting cancer by having early vaccination against congenital MSI.

Apart from tumor screening tests, family history is also very important in the diagnosis of LS. If there is evidence of LS in the family history, the risk of developing this syndrome increases by half. The risk of getting colon cancer due to LS increases by 80%\[^37\].

**Microsatellite Instability in CRC was first defined in 1993.\[^38,39\]**

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**COLORECTAL CANCER AND MICROSATELITE INSTABILITY**

Colorectal cancer is one of the most common types of cancer in all countries of the world. Colorectal cancers are generally located distal to the splenic flexure, the most important criterion in determining the prognosis in patients is the stage of the tumor.\[^40,41\]

While determining the stage of the tumor in CRCs; The questions such as which layer of the intestinal wall the cancer cells reach, whether they spread to neighboring tissues and organs, whether they show a spread to the surrounding lymph nodes, etc. are sought. While defining the stage of CRC, the tumor-node-metastasis (TNM) system is taken as the basis. According to this system:\[^40,42\]

- Which layers in the intestinal wall did the tumor involve and spread?
- Did the tumor involve the lymph nodes in the areas with tissue?
- Has cancer metastasized to other organs in the body? etc. Answers to questions are sought.

Colorectal cancers are thought to arise through two different mutational pathways named chromosomal instability or microsatellite instability. The pathway affecting chromosomal instability is characterized by mutations in the adenomatous polyposis coli (APC) gene located on the fifth chromosome (5q21). If the APC gene mutates, damage occurs during the separation of chromosomes, resulting in abnormal cell division.\[^40\] Chromosomal instability is a common feature in 85% of CRC cases, and its ability to be observed in even the smallest tumor indicates that it occurs in the early stages. APC gene mutations are among the most common causes of sporadic type CRC. Individuals with an APC mutation in their family history are always at higher risk of developing CRC. The microsatellite instability pathway is effective in the development of 15-20% of CRCs. If HNPPC, inactivation of one allele as germline and somatic inactivation of another allele; In sporadic CRC, there is somatic inactivation of both alleles. CRCs are divided into three groups in terms of MSI, and tumors with high MSI are named MSI-H, tumors with low levels are named MSI-L, and tumors with no MSI in any locus are called microsatellite stable (MSS).\[^43\] Patients with CRC with MSI features have different clinical and pathological features compared to those who do not. MSI has been identified as a positive effect in CRC-type cancers.\[^44\] It has been reported that the
possibility of metastasis is lower in tumor cases with MSI-H and the patient shows a better prognosis.\cite{45,46} It is known that patients with MSI-positive tumors show a better prognosis than patients with MSI-stable. In addition, the survival rate is high in individuals with MSI-H tumors.

**A BIOMARKER IN COLORECTAL CANCER TREATMENT; MICROSATELLITE INSTABILITY**

Currently, there are three biomarkers whose accuracy is accepted in the treatment of CRC. These are RAS, BRAF, and MSI. MSI has been characterized as both a prognostic predictor and therapeutic. MSI is commonly caused by epigenetic silencing of the MLH1 gene, thanks to frequent mutations in the BRAF oncone. During DNA synthesis, MMR proteins can repair mismatch errors with repeated base sequences called microsatellites, to maintain genomic stability. An incomplete or faulty MMR system causes protein losses that lead to the MSI phenotype.\cite{47} Germline mutations in MMR genes (MLH1, MSH2, MSH6, and PMS2) can lead to HNPCC formation or LS.\cite{47,48} Individuals with LS develop cancer earlier in age and rarely carry the BRAF mutation.\cite{49}

Microsatellite Instability phenotype is more common in stage II in CRCs. Microsatellite Instability begins to decrease as the metastatic environment improves.\cite{50} Therefore, in CRC cases, convenience is provided in the presence of MSI at the early diagnosis stage. Immunohistochemistry (IHC) or PCR-based methods are used to detect the presence of MSI in cancer cases. Microsatellite loci required for PCR are also determined over a system established.\cite{51}

In conclusion, cancer is one of the most important diseases of our age and CRC is one of the most common types of cancer. Genetic and environmental factors work together in the formation of cancerous cells. The presence of MSI, which is included in genetic factors, is a condition that is encountered in some cancer cases. If the patient has MSI, the PCR test to be performed at the first stage will facilitate the diagnosis of the disease in the early period. Or, people with a family history of LS-associated CRC vaccinated against cancer will reduce their risk of developing cancer. The ability to turn MSI, which is a mutation that occurs in the DNA repair system and increases the likelihood of cancer, into an advantage depends on scientific studies to be carried out by making the best of molecular techniques.

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**REFERENCES**

18. Bach SP, Gilbert A, Brock K, Korsgen S, Geh I, Hill J,


