CHAPTER

9

Metagenomic profiling of cancer-causing genes

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9.1 Introduction

Cancer, the term, is very much popular in today's health world. It is one type of illness that is characterized by uncontrolled growth of cells. It causes an abnormal cell mass or tumor, which is called malignancy. It might spread to various body sectors. Sometimes cancer is a genomic disease. There are two types of genes responsible for cancer. Oncogenes is one of them. It acts as a positive growth regulator (Ranjan et al., 2019). Another gene is known as the tumor suppressor gene, which acts as a negative growth regulator. In current days, malignancy is a significant health issue in both industrialized and developing nations. On World Cancer Day in 2012, the International Agency for Research on Cancer (IARC) published an international report on cancer. According to the report, it was indicated that there were 8.2 million cancer-related deaths, 14.1 million new cases of cancer, and 32.6 million people living with cancer (Banerjee et al., 2015). Mutations in the genes that regulate the body's normal functions are one of the leading reasons for the growth of cancer cells. Cancer may develop from different factors like genetic, environmental, lifestyle, etc. One of the important factors in developing cancer is microbes, which account for 16.1% of the total cancer cases globally (De Martel et al., 2012). Research has identified several microbes associated with different types of cancer. Cervical cancer is caused by the *Human papillomavirus* (HPV) (Zur Hausen, 1996), whereas *Helicobacter pylori* is responsible for gastric ulcers and Mucosa-associated lymphoid tissue (MALT) lymphoma (Cover & Blaser, 1873). Hepatitis B and C viruses are caused by Hepatocellular malignancy (Raza et al., 2007), and the *Merkel Cell Polyomavirus* is responsible for Merkel cell carcinoma (Feng et al., 2008). This kind of skin cancer is uncommon. Nasopharyngeal malignancy is caused by *Epstein–Barr* virus (EBV) (Goldenberg et al., 2004). The exploration analysis and interpretation of the microbial relationship with cancer have been revolutionized due to the expanding science

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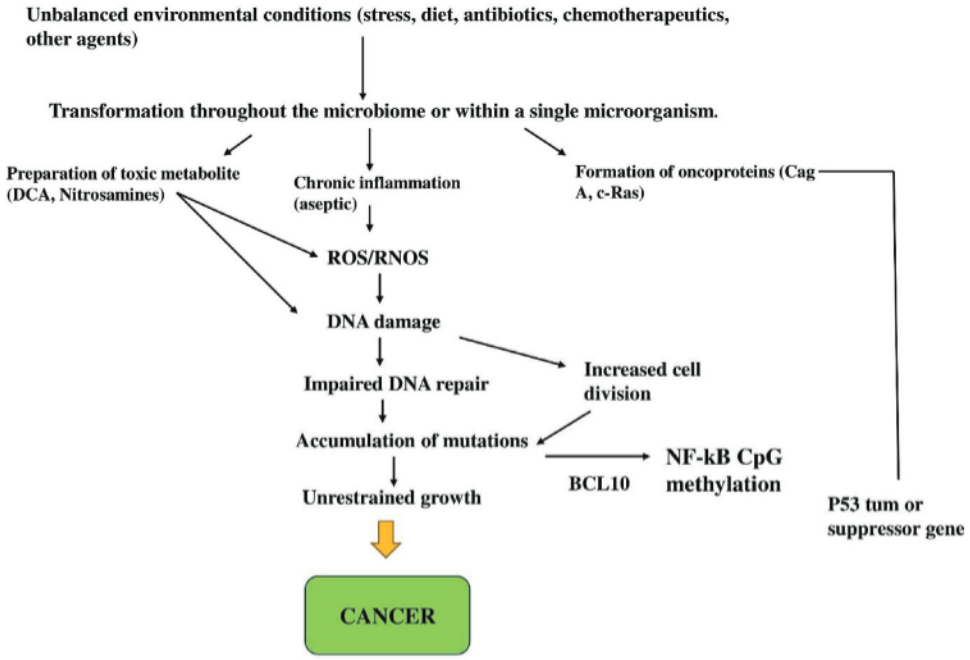

FIGURE 9.1 Oncogenesis mechanism brought on by alternations in the microbiome. The image illustrates that environmental imbalances lead to modifications in the normal microbiota, which cause the creation of toxic metabolites, chronic inflammation, and oncoproteins. *(From Chang, A. H., & Parsonnet, J. [2010]. Role of bacteria in oncogenesis. Clinical Microbiology Reviews, 23[4], 837–857).*

of metagenomics. It is a systematic method of researching culture-independent microorganisms, including their functions, structures, and interactions with their environment (Grossblatt & MacDonald, 2007). Current genomic studies of microorganisms in malignant tissue specimens have led to new insights into the role of microbes in cancer development.

According to a complete genomic study, the existence of *Fusobacterium sp.* and *Campylobacter sp.* was reported. A detailed assessment of colorectal cancer (CRC) bacteria was also provided (Castellarin et al., 2012; Kostic et al., 2012). A metagenomic study of prostate secretions revealed microbes from the Proteobacteria phylum (Smelov et al., 2014). Different metagenomics approaches have provided a new pathway for both preventing and treating microbe-associated malignancies. Prostate cancer is caused by *Escherichia coli* (*E. coli*) and *Propionibacterium acnes* microbes. Epidemiological research shows that 87% of affected patients have microbial DNA in their prostate (Alfano et al., 2016; Kwon et al., 2014; Shinohara et al., 2013; Simons et al., 2015). The oncogenesis mechanism is driven by alternations in the microbiome (Chang & Parsonnet, 2010). Fig. 9.1 represents the environmental imbalances that lead to microbiota modifications, creating toxic metabolites, chronic inflammation, and oncoproteins. Cancer cells develop when they proliferate uncontrollably due to the creation of DNA damage, free radicals, and damage of the p53 tumor suppressor gene.

TABLE 9.1 Overview of different microbes related to various cancer types.

Microbes	Triggered cancer
Human papillomavirus (HPV)	Cervical cancer (Zur Hausen, 1996)
Helicobacter pylori	Gastric cancer, MALT lymphoma, and oral cancer (Cover & Blaser, 2009; Dayama et al., 2011)
Epstein–Barr virus	Nasopharyngeal carcinoma (Goldenberg et al., 2004)
Merkel cell Polyomavirus	Merkel cell carcinoma (Feng et al., 2008)
Hepatitis B and C viruses	Hepatocellular carcinoma (Raza et al., 2007)
Human cytomegalo virus	Glioblastoma multiforme (Ranganathan et al., 2012; Soroceaunu et al., 2011)
Simian virus 40	Brain cancer (Pagano et al., 2004)
Streptococcus anginosus	Esophageal cancer and Head and neck cancer (Tateda et al., 2000)
Salmonella typhi	Gall bladder cancer and cholangiocarcinoma (Lazcano et al., 2001; Robbins et al., 1988; Wistuba & Gazdar, 2004)
Tropheryma whippelii	Extraintestinal lymphoma, lymphoma, and gastric adenocarcinoma (Cadenas et al., 1999; Gillen et al., 1993)
Mycoplasma penetrans	Kaposi's sarcoma (Barete et al., 2000; Tamburini et al., 2007; Wang et al., 1993)
Chlamydia trachomatis	Epithelial ovarian carcinoma (Quirk & Kupinski, 2001)
Chlamydia pneumoniae	Lung carcinoma (Kocazeybek, 2003)
Chlamydia psittaci	Ocular lymphoma (Ferreri et al., 2004)

The objective of this chapter is to highlight extensive research on metagenomic approaches related to cancer caused by microbes.

9.2 Historical opinions on the role of microorganisms in cancer

The knowledge that microorganisms are connected to cancer is not new. This was demonstrated by Francis Peyton Rous in 1911 through his well-known experiment with the Plymouth Rock hen. This experiment demonstrated the fact and presence of the Rous sarcoma virus (Rous, 1910, 1911). Rous received the Nobel Prize in medicine for discovering a remarkable tumor of RNA virus in 1966. According to Rous's discovery, mammalian tumor virus research was conducted extensively in 1930 (Becsei-Kilborn, 2010) Using an electron microscope, three scientists, Anthony Epstein, Bert Achong, and Yvonne Barr, found EBV particles in Burkitt's lymphoma cell line in 1964 (Epstein et al., 1964). The Nobel Prize in 2008 was awarded to Harald Zur Hausen for his research on the incidence of high-risk HPV genotypes in affected people with cervical malignancy and the apparent connection between HPV strains and disease (Zur Hausen, 1996). The list of microorganisms that can cause cancer is provided in Table 9.1.

9.3 Combining new sequencing techniques and metagenomics to fight diseases

Experimental studies on genomic sequencing of numerous harmful viruses have improved with an increased understanding of these species. Moreover, this microorganism research helped to identify the possible targets for antibacterial agents (Monaghan & Barrett, 2006), pathogenicity (Sakharkar et al., 2004), and resistance to antibiotics (Black & Hodgson, 2005; Field et al., 2004). Explaining the relationship between the microbiota and genome sequencing provided enhanced awareness of the illness. According to a report published by the committee of the US National Research Council, it was found that microbiological research on metagenomics has improved. It also provided a new window for looking into the previously unknown world of microorganisms and their diversity (Grossblatt & MacDonald, 2007). It has eliminated the necessity for species separation and laboratory cultivation (Chen & Pachter, 2005).

Over 99% of the microorganisms are still uncultivated and may not be fully demonstrated using standard methods based on laboratory culturing (Qin et al., 2010). A bacterial chromosome's 16S rRNA gene sequence has highly conserved and varied sequences. It is utilized in the metagenomics method to characterize microbial communities under various environments (Turnbaugh et al., 2009).

Significant studies have been done on metagenomic analyses of soil bacteria (Daniel, 2005; Dayama et al., 2011; Yooseph et al., 2013). Human microbes of the gut, oral cavity, and skin infection are very popular for research (Mardis, 2008). Additionally, the advancement of sequencing methods and techniques has been helpful in the investigation of the human microbiome in different body regions (Radford et al., 2012). Current developments in sequencing technology have promoted studies and assessments of the microbial genome.

9.4 Association between human microbiome and metagenomics

For every gram of excrement, the human stomach virus contains approximately a trillion bacterial cells (Gill et al., 2006). The human gut is a fundamental organ that regulates immunity, nutrition, metabolism, and physiology. Intestinal disorders, such as Crohn's disease, inflammatory bowel disease, and obesity, may have a direct connection to dysbiosis in the gut microbiome (Guinane & Cotter, 2013; Peterson et al., 2008; Tamboli et al., 2004). According to a recent study, distraction in the stomach infection causes age-related changes in humans. Similar to the human gut, the human oral cavity is inhabited by countless varieties of bacteria. Some of them are responsible for oral health conditions like tooth caries and periodontal disorders (Rampelli et al., 2013). In the periodontal swab samples, oral metagenomic research represented the existence of *Streptococcus sp.*, *Haemophilus sp.*, and *Capnocytophaga sp.* (Marsh et al., 2010). Similar to the oral and stomach cavities, human skin is inhabited by a variety of microorganisms. Skin microbiome disruption is the cause of the prevalence of dermatological disorders (Hannigan & Grice, 2013; Wang et al., 2013). When metagenome analysis was performed on sputum samples from people with the hereditary condition cystic fibrosis, it was found that there was a reduced occurrence of *Pseudomonas aeruginosa* (<1%) and a larger abundance of *Stenotrophomonas maltophilia* (41%–90%) (Lim et al., 2014). The genetic material of the database of microbial species connected to humans is referred to as the microbiome. The human body contains 10 to 100 trillion microbial cell communities, along with bacteria, fungi, and archaea (Althani et al., 2016). The most diversity of

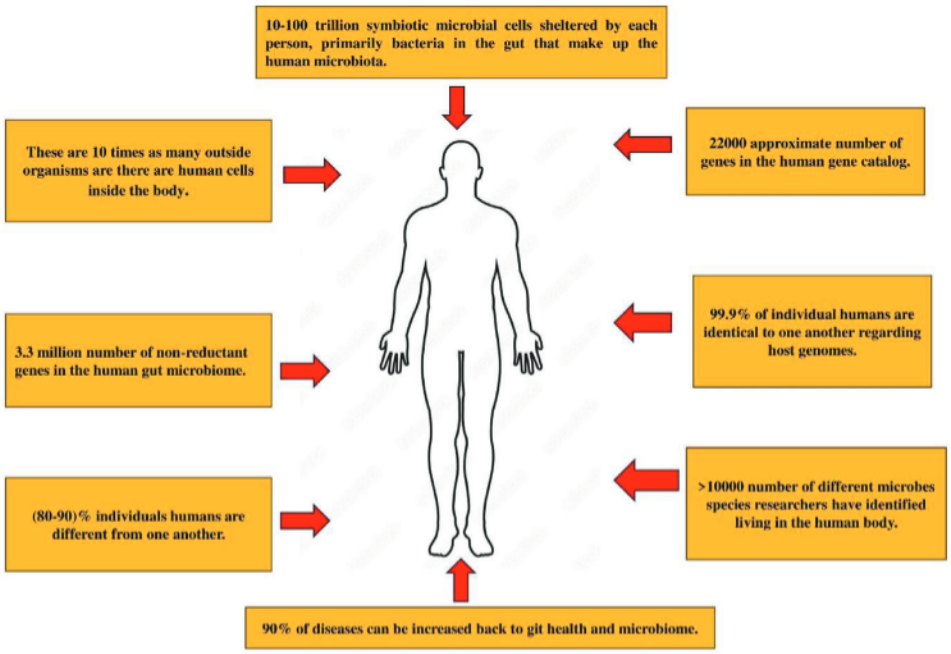

FIGURE 9.2 Illustration of the microbiota connected with humans. *(From Krishna, S. B., Dubey, A., Malla, M. A., Kothari, R., Upadhyay, C. P., Adam, J. K., & Kumar, A. [2019]. Integrating microbiome network: Establishing linkages between plants, microbes, and human health. The Open Microbiology Journal, 13[1] 330-342.)*

microbes was found in the gut. The connection between the human microbiota population and human health is still not completely known. However, different epidemiological studies found the relationship between the human microbiome and various human diseases like diabetes, gastric cancer, metabolic diseases, and lung cancer (Bakhtiar et al., 2013; Malla et al., 2019).

These studies proved that human microbes have an important role in defending against different microbial infections, metabolic process regulation, metabolic production, immune system preservation, and synthesis of vital nutrients (Rooney et al., 2020). Fig. 9.2 represents the different microbes associated with the human body. Metagenomics methods can classify microbe-based diseases, such as CRC, liver cirrhosis (CIRR), inflammatory bowel disease (IBD), bloodstream infections, central nervous system, etc. Various obstacles are found in diagnosing these microorganisms' pathogenic diseases. But it is continuing to overcome those problems with different new approaches.

9.5 Applications of metagenomics in the study of the human microbiome

There are uncountable human microbiome species that are still not discovered. It is not easy to understand the future of the microbiome. From current research, a powerful new independent method is found, known as Next Generation Sequencing Technology (NGS). This method has

been developed to identify the human microbiome through ecological analysis on a global scale (Allaband et al., 2019).

9.6 Metagenomic research on various types of cancer

9.6.1 Colorectal carcinoma

CRC is a complex disease, also known as CRC (Purcell et al., 2017). It represents one of the prevalent malignancies and has a high global death frequency. It has different medicinal results that respond to therapy. According to a previous study, it was almost found that 1.2 million patients are affected with CRC (Dejea et al., 2013), and the colon has extensive exposure to a wide variety of microorganisms (Warren et al., 2013). For women, CRC stands in second position (9.2%), and for males, it ranked third position (10%) among the leading causes of death (Stewart & Wild, 2013). Between 1990 and 2012, the incidence rate of CRC grew by over 200,000 new cases annually. In Western countries, most of the cases are identified (55%). Currently, this rate is varying due to the rapid development in specific countries (Brody, 2015). Due to advancements in health systems, only 33% of death incidents occur in Western nations (Cunningham et al., 2010). It is reported that every year almost 1.2 million patients are affected with colon cancer (CRC) worldwide (Dejea et al., 2013). Different research on gut-connected microbes, their interactions, and the incidence of stomach cancer may disclose the role performed by them for intestinal viruses. It has been found that structural variation in the gut microbiota is the factor that causes CRC to progress (McCoy & Mason, 1951). In 1951, McCoy and Mason proposed the connection between colonic cancer and the prevalence of *Streptococcus bovis/gallolyticus. Streptococcus bovis* was connected to colon cancer (Savage, 1977). Various researchers' genomic assessment of the CRC-infected tissue samples revealed an abundance of *Fusobacterium spp.*, especially *F. nucleatum, F. mortiferum*, and *F. necrophorum* (Castellarin et al., 2012; Kostic et al., 2012; Warren et al., 2013). *Fusobacterium* and *Campylobacter* are distinctly different from their oral counterparts in the tumor tissues. These gram-negative anaerobes are responsible for the mouth cavity (Neut et al., 2002). Another study revealed *Fusobacterium spp.* has been connected to inflammatory bowel diseases like ulcerative colitis and Crohn's disease (Sobhani et al., 2011; Strauss et al., 2011). In another research about CRC, tumors from patients with colon cancer have been found to contain a different population of *Clostridium leptum, Clostridium coccoides*, Bacteroides, *Lactobacillus spp., Bifidobacterium spp., E. coli*, and *Faecalibacterium prausnitzii sp.* (Fearon & Vogelstein, 1990).

9.6.1.1 Genomic pathways of colorectal cancer

CRC can develop due to mutation in particular genes. It happens in various cancers. Those mutations can appear in oncogenes, tumor suppressor genes, and genes associated with DNA repair pathways (Sobhani et al., 2011). According to the mutation's source, there are three types of colorectal carcinomas: sporadic, familial, and genetic. Point mutation only impacts specific cells and their progeny. They do not associate with inherited diseases and emerge during life. CRC can be categorized into three types: inherited (5%), familial (25%), and sporadic (70%). Sporadic tumors, which make up about 70% of all colorectal cancers, are malignancies caused by point mutations. Mutation may target many genes. There are several different biological pathways involved in sporadic cancer (Sobhani et al., 2011). Three different types of pathogenic ways can be identified as triggering the situation, known as CpG island methylator phenotype

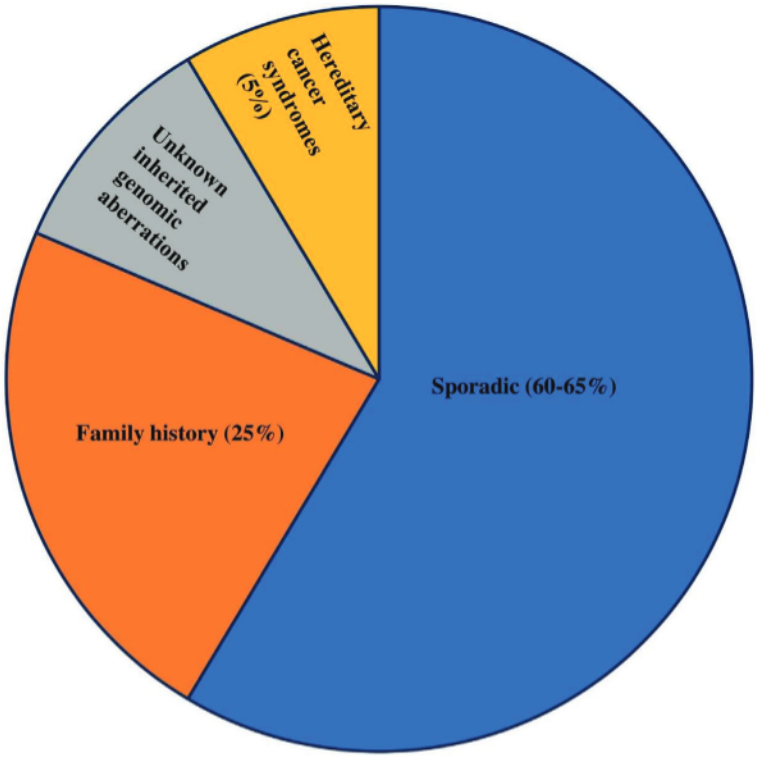

FIGURE 9.3 Pie chart showing the risk factor of colorectal cancer. *(From Keum, N., & Giovannucci, E. [2019]. Global burden of colorectal cancer: Emerging trends, risk factors, and prevention strategies. Nature Reviews Gastroenterology & Hepatology, 16[12], 713–732.)*

(CIMP), microsatellite instability (MSI), and chromosomal instability (CIN) (Mármol et al., 2017). Almost 70% of CRC cases indicate a particular morphological arrangement that begins with the development of an adenoma and concludes with the carcinoma stage. The initial mutation outcomes in the development of nonmalignant adenomas, generally known as adenomatous polyposis coli (APC). 15% of those adenomas will progress to the carcinoma stage. Other mutations are also found in KRAS, TP53, and DCC (Mármol et al., 2017).

9.6.1.2 Different risk variables of colorectal cancer

All over the world, almost 4% to 5% of humans are affected by colorectal cancer. Different human behavioral characteristics are considered as risk factors. They raise the possibility of developing colorectal polyps (Mármol et al., 2017). Age is one of the main factors of this cancer. The rate of infection is maximum above 50 years old, compared to below 50 (Eaden et al., 2001). Patients, who have ulcerative colitis, have a 3.7% increased chance of being affected by CRC (Canavan et al., 2006). IBD-related chronic inflammation frequently results in dysplasia, an aberrant proliferation of cells. Positive family history is one of the other factors included in this group. Due to inherited mutation in the environment, familial history is included as a risk factor (Johns & Houlston, 2001). Fig. 9.3 represents the risk factor of CRC with a pie chart.

Small lifestyle modifications in terms of food habits and exercise routines may help to decrease the risk factors. Though a specific relationship between inactivity and lifestyle, it is

thought that living a sedentary lifestyle increases the risk of cancer. However, different evidence showed that moderate physical activity reduces blood pressure and improves metabolic efficiency and gastrointestinal mobility.

9.6.2 Cervical cancer

Cervical cancer is an unwanted growth of cells in the cervix. It is the fourth most common cancer in women, which spreads worldwide. It signifies a global health challenge (Bray et al., 2018). Due to this cancer, the mortality rate increases rapidly. Almost 88% of cases were found in developing countries (Arbyn et al., 2011). High-risk HPV strains are caused by cervical malignancies. Therefore, vaccination and screening programs against HPV are useful tools for cancer prevention (Crosbie et al., 2013). The two most prevalent histological subtypes of cervical malignancies are squamous cell carcinoma (71%) and adenocarcinoma (25%). These are responsible for all types of affected cases (Ries et al., 1975; Small et al., 2017). Despite advancements in prevention, screening, diagnosis, and treatment, there have been significant variations in outcomes of cervical cancer (Cibula et al., 2018). Women's health is enhanced, and the pH of the vagina is lowered by the production of lactic acid by a healthy vaginal microbiota. This is made up of *Lactobacillus sp.* (Lee et al., 2013). *Bacterial Vaginosis* (BV) is characterized by the overgrowth of anaerobic bacteria and the loss of indigenous *Lactobacillus spp.* (Mancuso et al., 2011). It leads to an imbalance in the vaginal microbiota. This imbalance is associated with several harmful health conditions, including endometritis, elective abortions, pelvic inflammatory disease, vaginal discharge syndrome, and underprivileged pregnancy outcomes, etc. (Martin, 2012; Ness et al., 2005). Cervical cancer develops and progresses to a higher grade due to the persistence of HPV infection. Few forms of HPV infections carry a risk of cervical cancer (Koshiol et al., 2008). HPV can be divided into two different types with high-risk factors causing cervical cancer and low-risk factors producing benign infections (Zur Hausen, 2002). In the L1 main capsid area, there are over 200 HPV kinds with 90% sequence identity, and 118 types have their full genome sequenced (Bernard et al., 2010). The most carcinogenic HPV strains, HPV-16 and HPV-18, are thought to be almost always present in 71% of cervical cancer cases (Sanjose et al., 2010). An assessment study was found between HPV-positive and HPV-negative (Gao et al., 2013). It showed a connection between vaginal microbiota and HPV infection. This study represents the importance of *Lactobacillus spp., L. gallinarum, L. iners*, and *L. gasseri* in all women. In another research, it was found that the presence of a vaginal microbiome among Korean twins represented a lowered population of *Lactobacillus spp.* (Lee et al., 2013). Fig. 9.4 depicts the function of HPV genes (E6 and E7) in cervical cancer.

9.6.2.1 Epidemiological analysis

According to a study done in 2018, almost 569,847 new cases of cervical cancer were diagnosed and 311,365 death cases were found all over the world (Bray et al., 2018). It has been found that in high-income countries the rate of affected patients has decreased by more than half in the last 30 years (Anderson et al., 2020). According to research work, 38 countries in five continents represent a major decrease in age-based study in economically stable countries, while these rates have either stabilized or increased in low-income countries (Vaccarella et al., 2013). Cervical malignancy was the 11th most prevalent cancer in 2012. It is the 9th most common reason for cancer mortality in high-income countries. Statistically, the rate of affected patients was 9.9 million, whereas the death rate was 3.3 million (Waggoner, 2003). Women who lived in

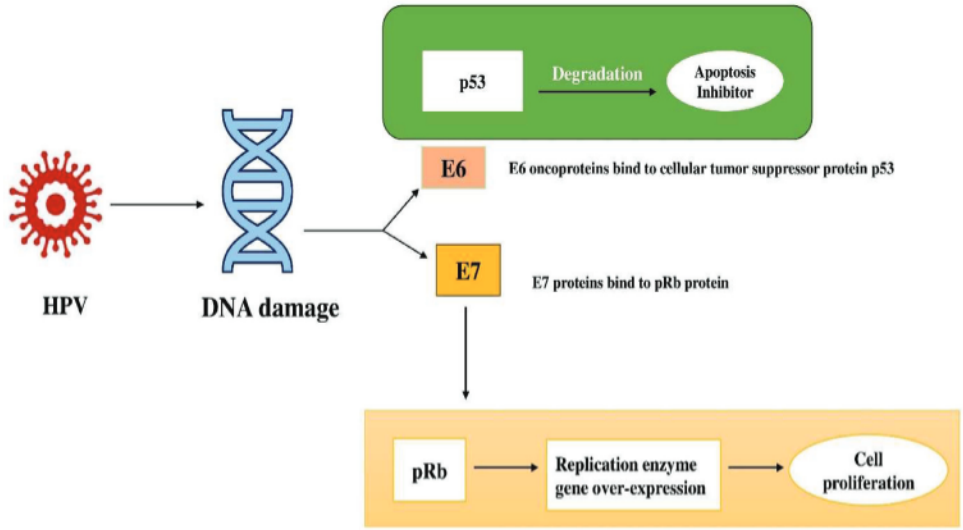

FIGURE 9.4 The involvement of human HPV genes E6 and E7 in the carcinogenesis of cervical cancer.

economically stable countries had a lifetime risk of 0.9% of developing cervical cancer. But, this rate for low-income countries is 1.6% (Olorunfemi et al., 2018). The median age of the affected patient in the United States is 47 years, and over 50% of cases are diagnosed before the age of 35 years (Olorunfemi et al., 2018). In South Africa, cervical cancer may be one of the main causes of death for women. Almost 25% of affected patients were aged 40 to 49 years (Fedewa et al., 2012). In a population-based study, nearly 70,000 cases of cervical cancer were detected. Most older women had a greater chance of having an advanced stage of cervical cancer (42.44% above 70 years and 16.53% for 21–34 years) (Cohen et al., 2019). Fig. 9.5 shows the scientific reason for cervical cancer.

9.6.2.2 Preventing method of cervical cancer

The primary method of preventing cervical cancer is to stay away from HPV infections. Although condoms are not 100% effective at avoiding infection. They can help prevent certain illnesses by not having sex, embracing mutual monogamy virgins, or abstaining from sexual activity. However, HPV vaccination is necessary for the initial prevention of cervical cancer, which is very effective. The efficacy of the first (bivalent) and quadrivalent HPV vaccinations, which are connected to high-grade cervical dysplasia, is greater than 90%. These HPV vaccinations were made available in 2006 (De Martel et al., 2012). A nine-valent vaccination that was introduced in 2018 has shown effectiveness in young women between the ages of 16 and 26 after six years (Hall et al., 2018). In those countries where HPV vaccination programs have started, incidence of cervical cancer has decreased (Brotherton et al., 2011). According to a previous study, Australia was the first country to introduce an HPV vaccination program (2007). The quadrivalent vaccine has (70%) coverage in girls and boys aged 12 to 13 years. Within 3 years of the vaccination program, high-grade cervical dysplasia in women under the age of 18 had decreased almost 38% (Drolet et al., 2015). In those countries where a minimum of 50% of the

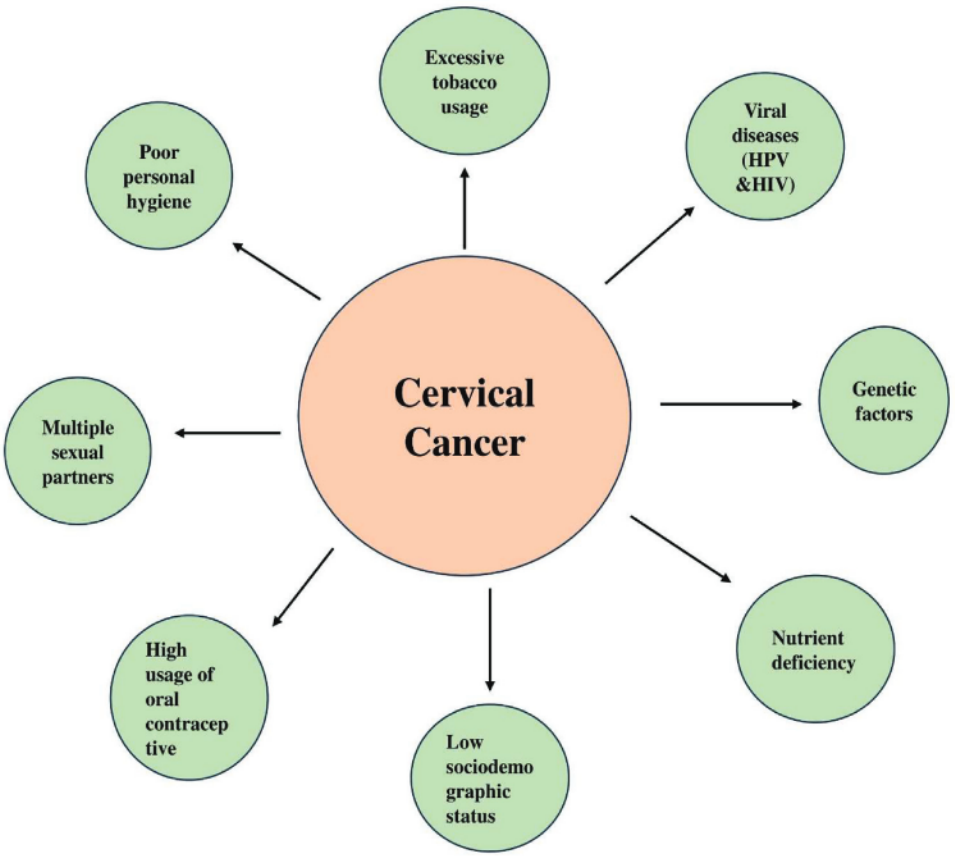

FIGURE 9.5 Different reasons for cervical cancer. *(From Huh, W. K., Joura, E. A., Giuliano, A. R., Iversen, O. E., de Andrade, R. P., Ault, K. A., & Luxembourg, A. [2017]. Final efficacy, immunogenicity, and safety analyses of a nine-valent human papillomavirus vaccine in women aged 16–26 years: A randomised, double-blind trial. The Lancet, 390[10108], 2143–2159.)*

total population was vaccinated, HPV 16 and HPV 18 infections decreased by 70% (Denny, 2015). The vaccination campaigns in low- and middle-income countries (LMICs) have been obstructed by cost, lack of adolescent health platforms, cultural barriers, and issues in reaching the target population (Denny, 2015).

9.6.3 Skin cancer

Human skin acts as a body barrier against the external world. Skin cancer is one of the common malignancies among humans. The incidence of skin cancer increases day by day. Although different skin cancer treatments are available, new studies and innovations are still required to decrease the number of affected patients. Recently, this type of cancer was detected in a million cases (D'Orazio et al., 2013; Rogers et al., 2010). Skin cancer is classified into three common types of malignancies. These are basal cell carcinomas (BCC), squamous cell

carcinoma (SCC), and cutaneous malignant melanoma (CMM) (Simoes et al., 2015). BCC and SCC are coming from keratinocytes. These two types are less infected than the other due to their propensity to restrict themselves to the major site of illness (Simoes et al., 2015). Most keratinocyte malignancies, which are catastrophic, develop on the face, arms, and other parts of the skin that are most exposed to ultraviolet light (D'Orazio et al., 2013; Narayanan et al., 2010; Rogers et al., 2010; Simoes et al., 2015). Moreover, these different types of skin cancers are the most prevalent kinds of cancer in people. It can cause severe deformity, which may hurt a patient's physical and mental health (Narayanan et al., 2010; Rhee et al., 2007; Suarez et al., 2007). Cutaneous malignant melanoma (CM) is the deadliest form of skin cancer. It is one of the metastasis-prone malignancies. It has affected patients significantly over the last few years (D'Orazio et al., 2013; Narayanan et al., 2010; Rogers et al., 2010; Simoes et al., 2015). This type of skin cancer is mainly detected in the body's head, neck, and lower parts (Gloster & Neal, 2006; Narayanan et al., 2010). It will be cured if it is diagnosed early. Different targeted therapies and immunotherapy have made improvements in the treatment of CM (Hodi et al., 2008,2010). Although, this malignancy is still causing problems if it spreads outside the original site (D'Orazio et al., 2013). Different factors are responsible for the increasing rate of skin cancer. UV exposure is one of the main reasons for this (Rigel, 2010). It has various hazardous effects that show direct and indirect mechanisms like oxidative stress and the production of cyclobutene pyrimidine dimers on the skin. According to current research, it is found that normal epidermal cells turn into malignant cells through different pathways like molecular profiles and anatomical distributions (Nikolaou & Stratigos, 2014; Whiteman & Green, 2011). Skin cancer can affect people with fair skin complexion as they haves lower levels of UV-blocking dark pigment. Due to epidermis sensitivity to UV radiation, people with lighter skin tones are more susceptible to UV-induced skin damage. These UV rays also harm skin cells and the deeper layers of the skin, which are known as keratinocytes and melanocytes. Fair-skinned people are more likely to be exposed to UV radiation and UV-induced mutations, which result in melanoma and other types of skin cancer (D'Orazio et al., 2013; Paulino et al., 2006). Other factors, like organ transplant Recipients and HIV patients have a chance of skin cancer. Different treatments may be responsible for skin malignancies, including phototherapy, radiation therapy, psoralen, and long-wave ultraviolet radiation (PUVA). Skin neoplasia may result from an imbalance in the usual microbial population of the skin. Significant research has demonstrated that microorganisms play an important role in noninfectious skin situations such as rosacea, psoriasis, acne, and atopic dermatitis (Mathieu et al., 2013; Till et al., 2000). According to previous research (Bzhalava and Dillner, 2013), the skin microbiome has been explored, and it was found that *Corynebacterium*, *Staphylococcus*, and *Propionibacterium* were the primary taxa that colonized the skin. In another research article about metagenomic analyses of human skin lesions, it has been found that 97% of HPV sequences were skin-prevalent (Feng et al., 2008). The presence of Merkel Cell Polyomavirus (MCPyV) in severe neuroendocrine skin cancer is particularly significant (Screening & Board, 2024; Shuda et al., 2008).

9.6.3.1 Prevention of skin cancer

Skin cancer protection against UV exposure is an important part of cancer prevention. To prevent skin cancer, one should avoid direct sun exposure between 10 am and 2 pm. People should use proper textiles with appropriate dressing and use proper sunscreens with a maximum sun protection factor of 15 to 20 (Trakatelli et al., 2007). Maximum sunscreen protects human skin

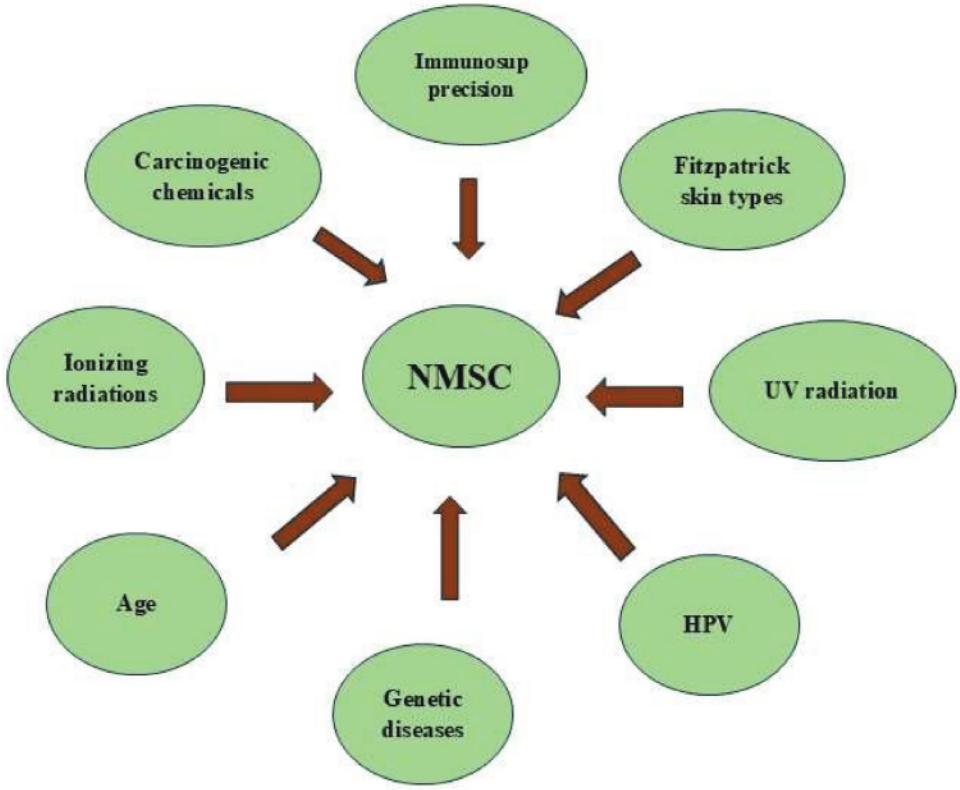

FIGURE 9.6 Different parameters involved in nonmelanoma skin cancer (NMSC) pathogenesis. *(From Didona, D., Paolino, G., Bottoni, U., & Cantisani, C. [2018]. Non melanoma skin cancer pathogenesis overview. Biomedicines, 6[1], 6.)*

from UVA and UVB radiation. Regular check-ups by dermatologists can help detect changes in skin color other early of skin cancer.

9.6.3.2 Diagnosis and screening for skin cancer

Histological control of the margins combined with surgical removal of all tumor cells remains the gold standard for treating skin cancer. Tumor thickness and the survival prognosis of patients with skin cancer, specifically melanoma, are negatively associated. Early detection and treatment are crucial for decreasing the morbidity rate of skin cancer. According to the current report, the nonmelanoma skin cancer mortality rate is higher than melanoma skin cancer (Soyer et al., 1987). Skin cancer screening is vital in lowering the number of affected patients. Different new approaches are applied to prevent skin cancer. Dermoscopy is one of them (Bafounta et al., 2001). It is a widely used method for skin cancer screening. This method significantly proves whether the type of cancer is benign or malignant (Binder et al., 1997; Vestergaard et al., 2008). Fig. 9.6 represents the different parameters involved in nonmelanoma skin cancer.

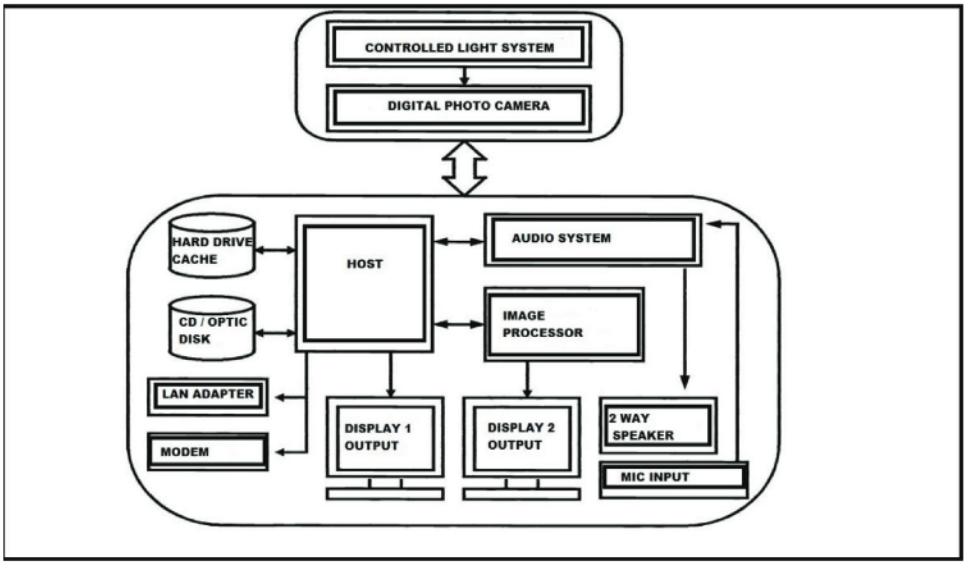

FIGURE 9.7 Block diagram of digital epiluminescence light microscope (DELM). *(From Fiorini, R. A., Crivellini, M., Codagnone, G., Dacquino, G. F., Libertini, M., & Morresi, A. [1997]. DELM image processing for skin-melanoma early diagnosis. In Applications of digital image processing XX [Vol. 3164, pp. 359–370]. SPIE.)*

Multiple instruments are applied in the screening process, which is costly and handled by experts. An epiluminescence microscope is used for the skin screening method, which provides a high-resolution lens with 12-fold magnification. The digital epiluminescence light microscope (DELM) and confocal laser scan microscope are used for the screening process. DELM is used for high melanoma skin cancer (Haenssle et al., 2004). As it has high sensitivity detection power, this instrument is used to detect early cutaneous melanoma skin cancer (Kittler et al., 2000). Fig. 9.7 represents the block diagram of the DELM device. It is a very useful device to detect and record melanocytic carcinoma. Reflectance confocal microscope known as confocal laser scanning microscope, has been used as a connection between dermoscopy and histopathological analysis (Stevenson et al., 2013). Its high-resolution technique may find the assessment of single cells of skin cancer (Seebode et al., 2016).

9.6.4 Oral cancer

Oral squamous cell carcinoma (OSCC) is a very popular carcinoma. Almost 90% of people are affected by this kind of cancer (Chen et al., 1999). In the past few years, the survival rate of OSCC has not been increased much in the overall 5 years. The complete survival rate is 56% whereas the virus-free survival rate is 58.2% (Bagan et al., 2010). The primary responsibility is to establish an early diagnosis during the initial phases of the illness (Bell et al., 2007;de Araújo et al., 2008).

For oral cancer patients, pain is a prevalent symptom that accounts for 30 to 40% of their primary complaints. The oral mucosa may be impacted by an extensive range of illnesses, either locally or as a symptom of a systemic condition. Different descriptions of pain were

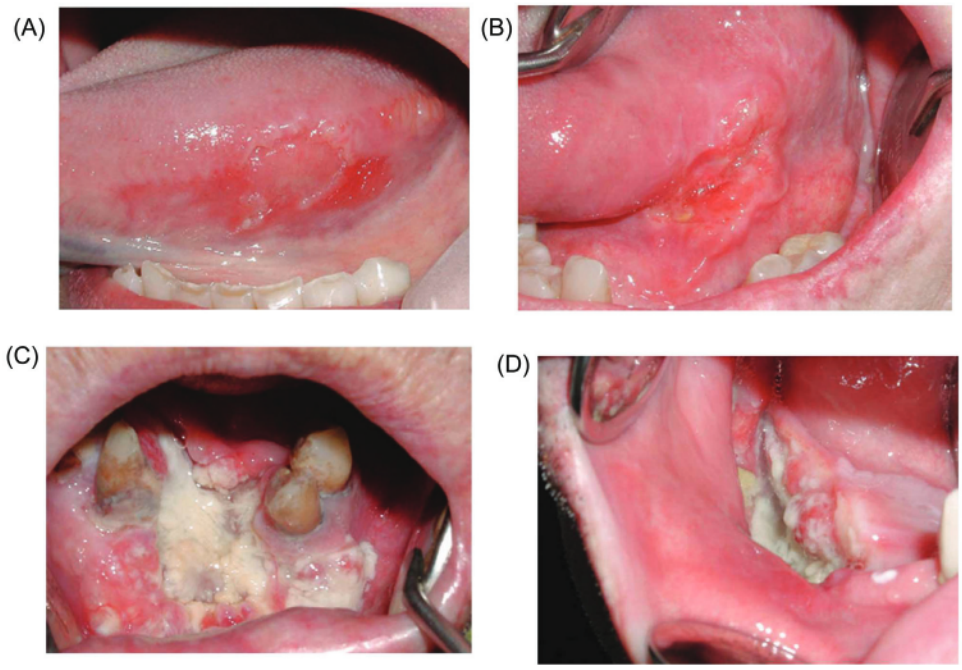

FIGURE 9.8 Pictorial representation of Oral cancer; (A) Oral cancer in the tongue, (B) Tumor in the lateral border of the tongue, (C) Tumor on the floor of the mouth, (D) Oral squamous cell carcinoma on the alveolar ridge. *(From Bagan, J., Sarrion, G., & Jimenez, Y. [2010]. Oral cancer: Clinical features. Oral Oncology, 46[6], 414–417.)*

found for those patients. Discomfort is connected to TNM staging in the tongue and mouth floor (Cuffari, et al., 2006). Discomfort is the primary symptom; it usually appears only after the wounds have grown quite large. At this point, the patient seeks medical attention. Initial carcinomas frequently go undiagnosed due to their lack of symptoms (Scully & Bagan, 2009). Symptoms of larger wounds may differ from moderate discomfort to excruciating agony, specifically when it comes to the tongue. Other different symptoms like pain in the ears, bleeding, tooth movement, breathing issues, and speech difficulties are found (Fernandez et al., 2004). In OSCC, tongue movement against the teeth becomes more uncomfortable. In the case of lip cancer and buccal mucosa, only intense pain is found (Barnes, 2005). According to the previous study, almost 52.6% of patients affected by OSCC have intense swelling in their teeth (Jainkittivong et al., 2009). Fig. 9.8 depicts OSCC in different parts of the mouth.

Human health is significantly impacted by the oral microbiome. Oral cancers and other oral disorders are often caused by harmful microorganisms that live in the oral cavity. The most important prerequisite is to understand the typical microbiota present in healthy individuals before it changes in the diseased state (Lazarevic et al., 2009). According to the previous study, it was found that salivary microbiome has been used as a method of diagnosis for oral malignancies. *Prevotella melaninogenica* and *Capnocytophaga gingivalis* of the microbiome were discovered by a well-known scientist (Mager et al., 2005). *Streptococcus mitis* of the firmicutes was identified by the same well-known scientist, which is responsible for OSCC

(Mager et al., 2005). Using next-generation sequencing, the first metagenomic analysis of the oral microbiome has been conducted on a single healthy individual sample (Xie et al., 2010). According to another study, the oral metagenome was investigated in a range of medical disorders using 454-pyrosequencing. By using V4-V5 16s rDNA-based 454 parallel DNA sequencing, it was possible to identify a comparatively modest percentage of *Mycoplasma spp.* in the saliva of patients with OSCC (Belda-Ferre, 2012). The saliva of these patients mostly contained a substantial inhabitant of Firmicutes and Bacteroidetes as well as unclassified bacteria (Belad et al., 2012; Pushalkar et al., 2011).

9.6.4.1 Oral cancer prevention method

To reduce the mortality rate of oral cancer, the primary prevention is that the use of tobacco and alcohol should be reduced. In low-income countries, to facilitate the use of tobacco and alcohol, the rate of them should be reduced. It should be unaffordable for locals. Apart from this, screening methods should be increased to decrease the rate of affected patients. Using opportunistic screening, a range of interventions was evaluated. Oral cancer surgeons, dentists, or other qualified healthcare providers carried out the visual inspection (Sankaranarayanan et al., 2015).

9.6.5 Brain cancer

In current days, brain cancer is very prevalent in the worldwide population. Abnormal cell development in the brain is known as a brain tumor. Two types of brain tumors happen in human beings. One type of tumor is noncancerous, which is benign in nature. They are not easily spread to other parts of the body. A benign tumor may grow with time, creating pressure on the other brain cells. Another type of tumor that can easily spread all over the body along with the brain, is known as malignancy. This type of tumor grows rapidly and destroys other tissues. Despite major advancements in the treatment of many other cancers, brain tumors remain a deep and unresolved clinical concern. There are almost 43,800 cases found in the United States, and 18,500 are expected to be malignant (American Cancer Society, 2004; Cosset et al., 2014; Dolecek et al., 2012; Ullrich & Pomeroy, 2003). Early detection of intracranial cancer is still challenging to identify and treat. The fact that multiple brain tumors are located inside or adjacent to anatomical areas. Their activities complicate other tissues. Presently, an invasive biopsy is one of the successful methods to confirm the treatment of cancer. These methods provide different information about histological features, grade, differentiation, the possibility of aggression, and other information that helps to determine the best treatment. Different imaging approaches, such as CT, PET ultrasound, and MRI, are quickly used for identifying tumors and malignancies. For the treatment of malignant tumors, chemotherapy/radiotherapy is used. Even with recent advancements in brain tumor surgery and adjuvant treatment, the multimodality strategy is now utilized in the surgical therapy of malignant brain tumors. However, this advancement is not so much fruitful for affected patients (Holland, 2000). A grade 4 type of brain cancer with a terrible prognosis, glioblastoma multiforme (GBM) originates from glial cells in the central nervous system. It is a very violent and serious condition (Butel & Lednicky, 1999; Zhu & Parada, 2002). Brain tumors have been connected to the aggressive oncogenic DNA virus known as the polyomavirus simian virus 40 (SV40) (Pagano et al., 2004; Ranganathan et al., 2012). It has been found that SV40 causes primary brain neoplasia in animal models in addition to other cancer forms like malignant mesotheliomas, bone tumors, and systemic lymphomas

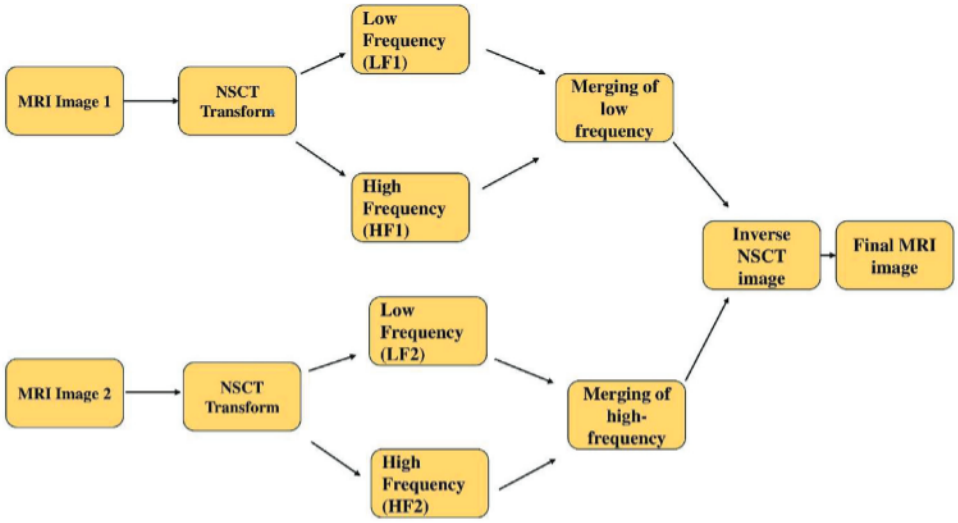

FIGURE 9.9 Schematic diagram of MRI image. *(From Paiva, W. S., Fonoff, E. T., Beer-Furlan, A., Morais, B. A., Neville, I. S., Ramos-Filho, R. B., & Teixeira, M. J. [2019]. Evaluation of postoperative deficits following motor cortex tumor resection using small craniotomy. The Surgery Journal, 5[01], e8–e13.)*

(Dziurzynski et al., 2012). According to a previous study, there is a strong correlation between brain tumors and the human cytomegalovirus (HCMV). With the help of quantitative real-time PCR on the GBM samples, the genomic analysis revealed that all of the sections were present in the HCMV genome (Ranganathan et al., 2012). Most GBM cases had viral gene expression and the presence of CMV sequences, as proved in a recent study (Dziurzynski et al., 2012). Fig. 9.9 represents the schematic diagram of an MRI image (Paiva et al., 2019).

9.7 Conclusion

Metagenomics has expanded the field of microorganism studies in their natural environments. Next-generation sequencing methods have strengthened the current updating of this area of study. Since microorganisms cause a significant portion of tumors, metagenomics research can help in the fight against cancer by identifying the microbes that cause the disease. Since the last 30 years, significant progress in this field has been made. To determine the underlying mechanisms of the microorganisms, it is required to understand the structure, diversity, richness, and dynamics of them. However, for a thorough study, it is essential to incorporate data from the microbial community and its associated environment. The macro dynamics of physical environments and the interplay among their elements directly influence the microbiological world. To understand the physical, chemical, and relational aspects of micro-inhabitants more insightful prediction is required. Although, with the advancement of science, it is possible to reach memorable milestones, scientists are still facing many challenges in microbial science. Different bioinformatic software is required to investigate the metagenomic analysis. To interpret more data, updating the software is urgently required. Current problems in metagenomics are

classified into two groups. One is to develop novel bioinformatic software. Another one is to generate new molecular applications. Gene target identification rates are often low for current functional screening techniques. Enhancing the screening effectiveness of metagenomic data sets requires the development of novel synthetic circuits, which are capable of detecting enzymatic activities. In this way, it will be possible to incorporate new ideas into the metagenomics science. Thereby, to improve current knowledge a wide range of combined efforts are collected by specialists to overcome the previous problems. Discovering possible targets in cancer studies will improve preventative measures and improve the scope of the field. Therefore, future research on the cancer microbiome for different cancer types is advised.

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Non-Print Items

Abstract

Metagenomic techniques, used to apply a wide range of genomic technologies and bioinformatics methods, provide direct access to the genetic structure of entire organism communities. Over the past few years, metagenomics has significantly advanced microbial ecology, evolution, and numerous research laboratories. Since the beginning of metagenomic research, a completely new (micro) universe has been revealed. The advancement of the metagenomic method has expanded the chance of targeting viruses that trigger different kinds of malignancies. Almost 16.1% of malignancies are caused by microbial infection. Metagenomics is an impartial method of discovering and analyzing viruses with their original characteristics. This approach has completely altered microbiological diversity. It is observed in cancer cells identified, analyzed, and targeted in cancer research. Identifying the microbial inhabitants in biospecies and their biological interactions with one another is helping us to understand the genomic analysis of these microorganisms. Using next-generation sequencing techniques, it becomes easier to learn. Numerous microbes have been discovered to be associated with different types of malignancies, which has greatly advanced the understanding of the disease at the molecular level. Metagenomics has created a strong framework that helps comprehend the complex relationship between microbial populations and human culture. Based on statistical studies, microbial infection has been related to 16% of cancer cases. Consequently, researching the metagenomics of cancer patients' tumor tissues will help scientists to understand the function of the microbes in the therapeutic response. In this chapter, an effort has been made to produce a recent metagenomic technique associated with cancer microbiota.

Keywords

Bioinformatics; Gene Sequence; Genomics; Malignancy; Metagenomics, microbiome