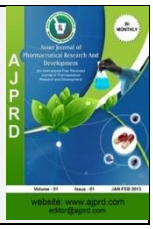
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Review Article

Effect of Covid-19 in Management of Lung Cancer Disease: A Review

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ABSTRACT

COVID-19 outcomes may be more severe in lung cancer patients. As a COVID-19 pandemic spreads, it's critical to identify which people and malignancies are most susceptible. COVID-19 appears to have the worst results in lung cancer patients. Lung damage or reduced lung capacity can be caused by the disease itself or by cancer treatments such as radiation and surgery. The earlier lung cancer is diagnosed, the better the prognosis. As a result, early detection technology for cancer is in high demand. Early diagnosis in large population screens is closely connected to non-invasiveness and cost-effectiveness. As a result, microelectronic-based sensor technology may be used to construct sensitive biomarker detection systems. Various biosensors have recently recognized cancer-related proteins. Researchers are increasingly interested in testing for volatile metabolites found in the breath. Companion testing for innovative anti-cancer drugs and re-biopsy for new therapeutic uses are helping to speed up the development of lung cancer diagnostic tests. This review covers all current lung cancer diagnostic modalities in depth.

Keyword: Covid19, Lung cancer, receptors, pathways, inhibitors, biosensors

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INTRODUCTION

The term "cancer" includes all forms of cancer. Tumours and Neoplasms are interchangeable. One of the most essential features of cancer is the rapid proliferation of abnormal cells that can invade and spread to other parts of the body. Cancer fatalities are usually caused by metastasis. More than half of all cancer deaths occur in low- and middle-income countries. Tobacco,

obesity, alcohol, a poor diet, and inactivity all contribute to one-third of cancer-related deaths. 30 percent of cancer cases in low- and middle-income countries are caused by cancer-causing illnesses including hepatitis and HPV (HPV). Lack of access to diagnosis and treatment is common in low- and middle-income countries. A study found that comprehensive treatment is available in over 90% of high-income countries but less than 15% in low-income countries. Cancer has a rising impact on the economy. Cancer will cost the world economy $2.16 trillion yearly by 2020. A precancerous lesion evolves into a malignant tumour when normal cells become cancerous. Infections from specific viruses, bacteria, or parasites interact with a person's genetic variables to cause these alterations. The World Health Organization's International Agency for Cancer Research (IARC) categorises cancer-causing chemicals (WHO). Cancer incidence increases with age due to the accumulation of cancer-related risks. The fact that cellular repair mechanisms grow less effective with age increases a person's total risk of illness. The WHO says developing nations must enhance cancer care (WHO). The World Health Organization predicts a 60% increase in cancer incidence over the next two decades if current trends continue. Survivance rates are predicted to fall further in low- and middle-income countries (an estimated 81 percent). Because their health systems are unprepared to prevent, detect, and cure cancer, many countries have been compelled to prioritise infectious diseases and maternal and child health.

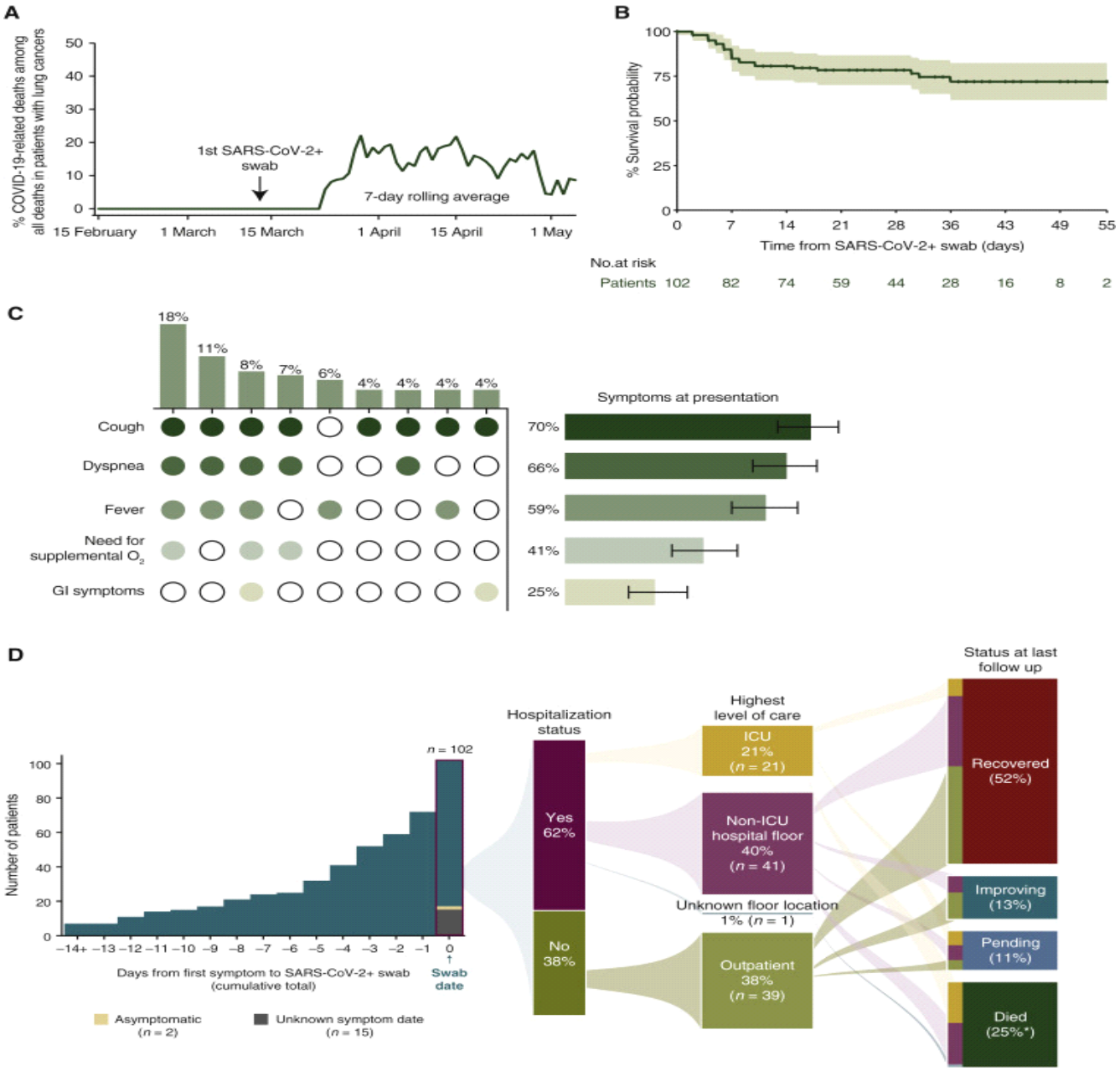


Figure 1: Clinical impact of COVID 19 in lung cancer patients

In 2019, public health systems in high-income countries provided complete cancer treatment, compared to less than 15% in low-income countries. Most nations (94%) reassigned NCD-related ministry of health staff to COVID-19. More than half of countries reported delaying public breast and cervical cancer screening. Reducing non-urgent facility-based therapy was first recommended by WHO. Reduced public transit and personnel shortages owing to COVID19 services were the most common reasons for terminating or curtailing services. One in five nations (20%) experienced service disruptions owing to medication, diagnostic, and technological shortages.

Unsurprisingly, service interruption appears to be linked to the spread of COVID-19. Services are impacted as a country shifts from sporadic to communal transmission. NCD services were incorporated in high-income (72%) and low-income (42%) COVID-19 preparedness and response plans. The most prevalent services were for heart, cancer, diabetes, and lung disorders. Dental care, rehabilitation, and smoking cessation programmes were not as prevalent.

HH Signaling pathways

Humans and Drosophila carry a variety in the HH signalling pathway, notably in signal transduction processes. This pathway is essential for embryonic cell proliferation, differentiation, and tissue polarity maintenance. This protein promotes adult stem cell renewal, organ homeostasis, tissue repair, and oncogenesis. The three human homologous HH ligand proteins — "Sonic," "Indian," and "Desert" — evolved from one Drosophila HH protein. However, each protein is synthesised in a different organ and reacts differently with receptors. The SHH, expressed in many tissues, including the digestive system, is the most studied. The endoplasmic reticulum auto-processing mechanism in Drosophila and mammals is quite similar. Skinny HH in Drosophila catalyses the translation of the HHAT gene into an enzyme that functions in the secretory system. In the nucleus, GLI transcription factors promote the transcription of many target genes, including GLI1 and PTCH1, proliferation-promoting genes Cyclin-D1 and MYC, cell cycle regulators CCND2 and CNE1, apoptotic regulator bcl2, and angiogenesis, angiogenic transition, and stem cell self-renewal genes NANOG and SOX2. The pathway's outcome is governed by the activator/repressor GLI protein ratio. Primary cilia are required for mammalian HH signalling to activate GLI transcription factors. Mammalian primary cilia include PTCH1 and PTCH2. On the cilia, GLI3 suppression is blocked by the Kinesin protein KIF7. Patched receptors prohibit SMO from migrating to primary cilia when it is not attached to a ligand. In these conditions, KIF7 is found in the proteasome-rich basal body of the main cilium. GSK3, PKA, and Kif7 all phosphorylate GLI 2 and 3. This causes GLI3 and GLI2 to be proteolytically repressed, preventing transcription. SuFu inhibits the pathway in a big manner. It blocks GLI protein entry into the nucleus by directly attaching to them. SuFu binds to GLI-binding DNA sequences in the nucleus and blocks gene transcription. A transmembrane protein reduces HH signalling. This protein's HH-ligand binding promotes endocytic endocytosis. 1 shows the human HH signalling system in both ON and OFF modes.

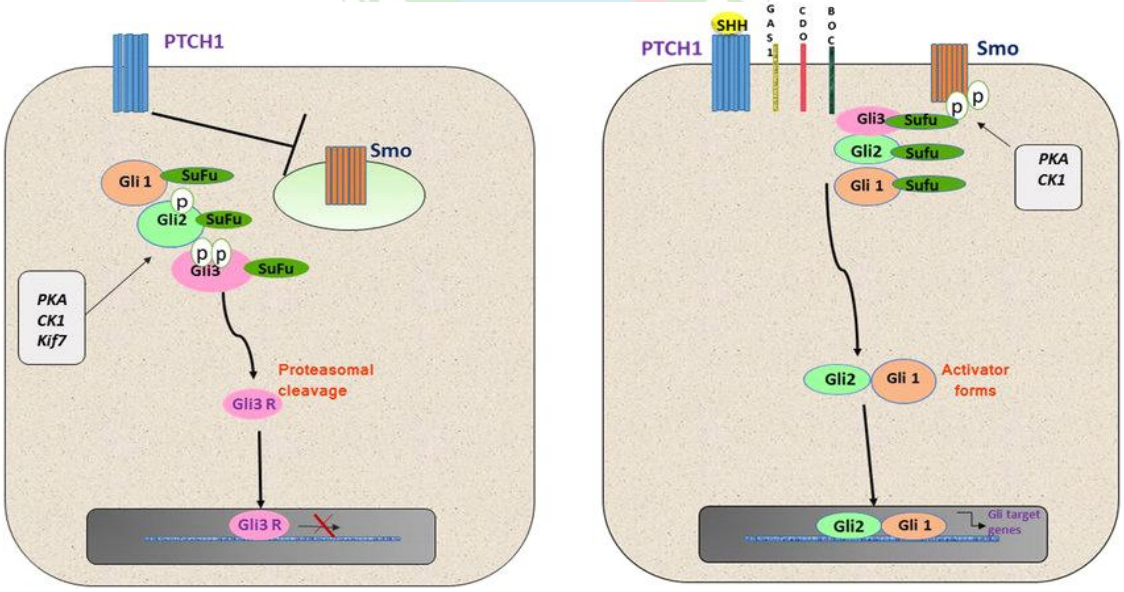


Figure 2: Diagrammatic Signaling Pathways of HH

Role of Mucins in Lung Cancer

Mucins produced by goblet cells inside the epithelia protect the lungs and alveoli against exhaustion, pathogen invasion, and chemical agents. In a healthy airway, MUC1 expression is low and diffuse. MUC1 is absent from submucosal glands and bronchial mucosa. The respiratory epithelium expresses modest MUC2, but the basal pole of certain goblet cells expresses significant MUC2. MUC2 is not found in bronchioles or alveolar epithelial cells. But MUC4 is expressed by most respiratory epithelial cells, including basal and ciliated cells. MUC4 expression is

trong in alveolar epithelium and submucosal glands. This mucin is considered to have a function in the differentiation of all respiratory epithelial cells and is created in the lungs as early as 6.5 weeks after conception. MUC4 appears in pregnant women's lungs about 12 weeks gestation. MUC5AC expression in segmental bronchial epithelial buds begins during the 13th week of pregnancy. The trachea and main bronchi have high MUC5AC expression, but not the smaller bronchioles or alveolar epithelial cells. MUC5AC is present on the surface epithelium, glandular ducts, and goblet cells. During 13 weeks of gestation, this gene is detected in bronchial epithelium, submucosal glands, and glandular ducts. MUC5B lacks alveolar epithelium, however it is abundant in collecting duct and submucoid cells. MUC7 is only present in the serous cells of various submucosal glands. Other mucins like MUC3 and MUC6 are absent from respiratory mucosa.

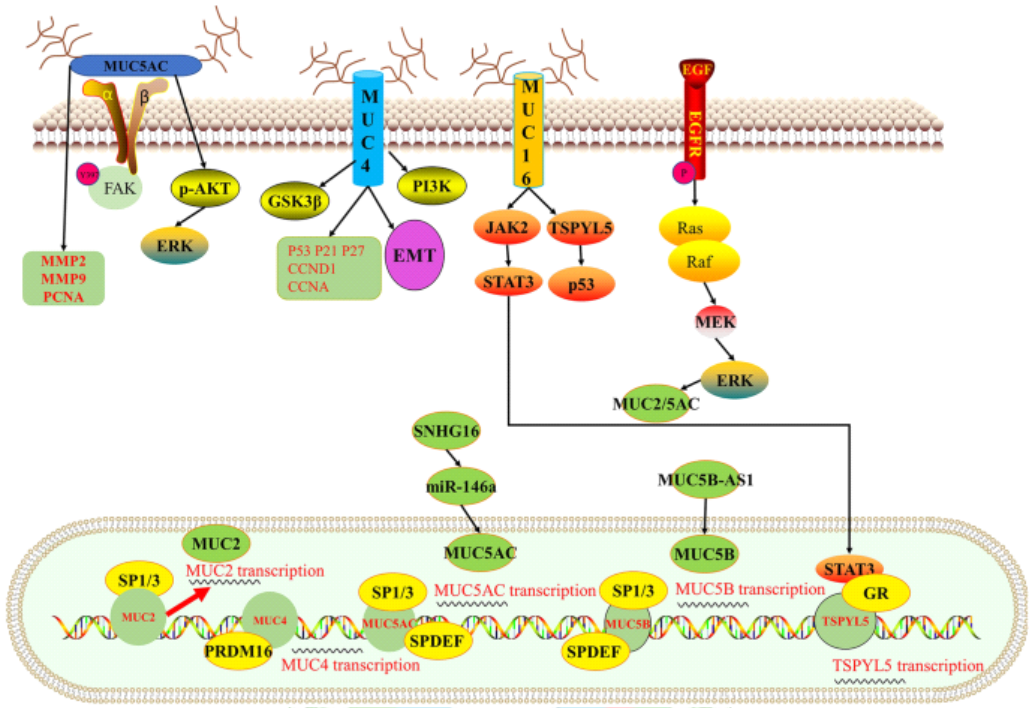


Figure 3: Mucins signaling in beginning and pathogenesis of Lung Cancer

Imaging studies for detection of lung cancer

Various imaging methods can be used to diagnose and stage lung cancer. In the real world, correct diagnosis needs multiple imaging tests.

Chest CT

CT Scanning is a vital imaging method for lung cancer detection and staging. This approach can classify and size lung lesions surrounded by air-filled lung tissue. CT scans can also reveal mediastinal lymphadenopathy, pleural effusion, and liver metastases. Korea has started employing low-dose chest CT for high-risk lung cancer screening since September 2019. LDCT, rather than chest radiography, improves the prognosis of lung cancer patients. The Nationwide Lung Cancer Screening Trial demonstrated that LDCT screening decreased lung cancer death for high-risk groups by 20% compared to chest X-ray screening. Further diagnostic tests should be conducted on patients with positive LDCT results.

PET-CT

PET-CT is a nuclear medicine technology that combines CT and PET scanning. The fusion image may be used to reproduce 2D and 3D pictures utilising common software and control systems. It enhances anatomical placement precision, therefore enhancing medical diagnostics. Oncologists now use PET-CT to diagnose and categorise cancers. In nuclear medicine departments, PET-CT has increasingly displaced standard PET equipment due to its therapeutic impact. PET-CT is too costly. Making and delivering short-half-life radiopharmaceuticals for PET imaging is similarly difficult (e.g., radioactive fluorine-18). 106 minutes of fluorodeoxyglucose employ pricey cyclotron and radiopharmaceutical lines.

Brain Magnetic Resonance Imaging

MRI can currently identify tumours 4 mm or larger with strong spatial resolution in lung cancer diagnosis and therapy. Breath holding and/or gating have been utilised in the past to reduce respiratory motion artefacts. This isn't the norm. A lung cancer imaging scan now takes less than 20 seconds. Withholding air for 20 seconds increases the risk of unintentional movements. The necessity for respiratory and ECG gating in lung cancer imaging may be avoided. Large-field-of-view MR scanners are more sensitive and take up more signals. Parallel imaging and compressed sensing have significantly sped up MR imaging captures in recent years. Using individual coil elements in multi-channel radiofrequency receiver arrays or transmit/receive coil arrays reduces the number of phase encoding steps in imaging. Parallel imaging requires multi-

channel RF coil array performance. Compressed sensing algorithms have recently been developed to dramatically speed up picture capturing from undersampled data sources. Compressed sensing can be done with radiofrequency coils or multi-channel radiofrequency arrays. The requisite wide field of view and present radiofrequency coil array technologies make it challenging to shorten acquisition time for lung imaging to 5 seconds or less. Parallel imaging, compressed sensing, and image optimization must be coupled. Lung imaging need a multi-channel radiofrequency (e.g. 32- or 64-channels). Large-channel radiofrequency coil arrays provide a substantial design challenge. The most successful options are magnetic barriers or induced current compensation or elimination (ICE) decoupling technology. Parallel imaging is five to six times quicker than a 32 or 64-channel RF coil array. Compressed sensing or its derivatives can speed up the process by a factor of four. Parallel imaging may boost total imaging speed by 20 times when combined with today's 32 or 64 channel RF technology. Without ECG gating and unrestricted breathing, this might reduce acquisition time to 5 seconds or less.

Neurotransmitters and Associated Receptors

Tumour tissue contains a distinct form of stem cell-like cell known as CSCs (Cancer Stem Cells). Cancer cells can form when stem cells self-renew95. Their involvement in cancer initiation, development, metastasis, and resistance to treatment is still a mystery95. Pancreatic cancer stem cells secrete and release Epi, Nor, and GABA into the culture media following cell sorting or selective culturing procedures. Stem cell self-renewal was facilitated by chronic nicotine exposure that enhanced stress neurotransmitter release and decreased GABA levels. The effects of GABA therapy were completely reversed. SHH's downstream effector GLi1 and aldehyde dehydrogenase-1 (ADH1) are upregulated in stem cells of non-small cell lung cancer (NSCLC) (ALDH-1). GABA or dynorphin B inhibited the formation of cAMP5 in cells.

Table 1: Inhibitors of the formation, progression, and resistance to treatment of Camp-driven malignancies are available.

Agents	Mechanism of Action	Sources
GABA	Inhibits Camp formation via G –protein	Nutritional, red wines, tomatoes,
Opioids Peptides Dynorphins, endor Opioids Methadone	Inhibits Camp formation G- coupled opioids receptors	Anesthesia, analgesia , cough suppression, management of addiction
Cannabinoids	CB1, CB2 release	Medical marihuana , synthetic cannabiniods receptors
Valerian GABA-B-R PAMS Stress reduction happiness	GABA synthesis by induction of GAD enzymes Positive allosteric modulators of GABA –B receptors Increase endogenous GABA and Opiods peptides while reducing epinephrine/ non epinephrine	Non prescription herbal root extract used as sleep aid and anxiolytic Therapeutic for addiction Methods to achieve this psychological state vary for each individual

Biosensors for Biomarkers

Biosensors work by immobilising antigens, antibodies, and DNA strands on an inorganic sensor surface. The receptor loses its three-dimensional structure when immobilised. Damaged sensors lose their ability to recognise chemical molecules. The complexity and fragility of biomolecules may lead biosensors to be unstable and short-lived.

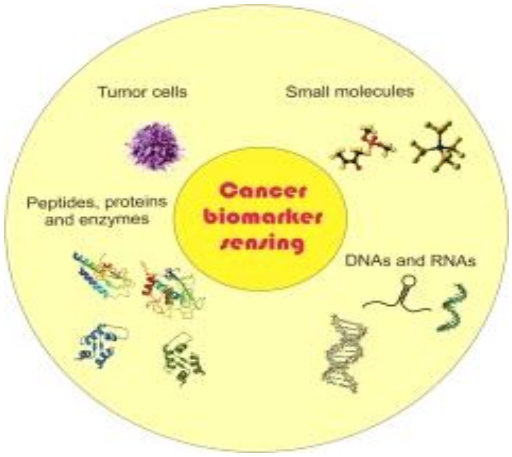


Figure 4: Detection of Lung Cancer Biomarker through Biosensor Technique

Although the field of biosensors is still in its infancy, fascinating discoveries are expected to be made in the future. Immuno selective interactions can be detected with no label. Antigen-coated gold nano particles have been developed. There was a detection limit of 1 ng/mL. Dickkopf-1, a lung cancer protein, may be detected with this method without the need for labelling. Non-small cell lung cancer can be diagnosed and treated with the use of an EGFR mutation. Immune checkpoint blockade may be influenced by other oncogenes. Compared to immunotherapy, tailored treatment proved to be more effective for these patients. Using tissue next-generation sequencing, researchers discovered ARID1A mutations linked to longer progression-free survival in NSCLC.

DISCUSSION

The term "cancer" includes all forms of cancer. Tumours and Neoplasms are interchangeable. One of the most essential features of cancer is the rapid proliferation of abnormal cells that can invade and spread to other parts of the body. Cancer fatalities are usually caused by metastasis. More than half of all cancer deaths occur in low- and middle-income countries. Tobacco, obesity, alcohol, a poor diet, and inactivity all contribute to one-third of cancer-related deaths. 30 percent of cancer cases in low- and middle-income countries are caused by cancer-causing illnesses including hepatitis and HPV (HPV). Lack of access to diagnosis and treatment is common in low- and middle-income countries. A study found that comprehensive treatment is available in over 90% of high-income countries but less than 15% in low-income countries. Cancer has a rising impact on the economy. Cancer will cost the world economy $2.16 trillion yearly by 2020. A precancerous lesion evolves into a malignant tumour when normal cells become cancerous. Infections from specific viruses, bacteria, or parasites interact with a person's genetic variables to cause these alterations. The World Health Organization's International Agency for Cancer Research (IARC) categorises cancer-causing chemicals (WHO). Cancer incidence increases with age due to the accumulation of cancer-related risks. The fact that cellular repair mechanisms grow less effective with age increases a person's total risk of illness. The WHO says developing nations must enhance cancer care (WHO). The World Health Organization predicts a 60% increase in cancer incidence over the next two decades if current trends continue. The most prevalent services were for heart, cancer, diabetes, and lung disorders. Dental care, rehabilitation, and smoking cessation programmes were not as prevalent. . SuFu binds to GLI-binding DNA sequences in the nucleus and blocks gene transcription. A transmembrane protein reduces HH signalling. This protein's HH-ligand binding promotes endocytic endocytosis. 1 shows the human HH signalling system in both ON and OFF modes. The receptor loses its three-dimensional structure when immobilised. Damaged sensors lose their ability to recognise chemical molecules. The complexity and fragility of biomolecules may lead biosensors to be unstable and short-lived. Immuno selective interactions can be detected with no label. Antigen-coated gold nano particles have been developed. There was a detection limit of 1 ng/mL. Dickkopf-1, a lung cancer protein, may be detected with this method without the need for labelling. Non-small cell lung cancer can be diagnosed and treated with the use of an EGFR mutation. Immune checkpoint blockade may be influenced by other oncogenes. Compared to immunotherapy, tailored treatment proved to be more effective for these patients. Using tissue next-generation sequencing, researchers discovered ARID1A mutations linked to longer progression-free survival in NSCLC. pleural effusion, and liver metastases. Korea has started employing low-dose chest CT for high-risk lung cancer screening since September 2019. LDCT, rather than chest radiography, improves the prognosis of lung cancer patients. The Nationwide Lung Cancer Screening Trial demonstrated that LDCT screening decreased lung cancer death for high-risk groups by 20% compared to chest X-ray screening

CONCLUSION

Biosensors are unrivalled in their illness detection. MUC1 alters the environment and genetic makeup of cancer cells to promote metastatic growth and spread. For MUC1-targeted lung or pancreatic cancer patients, the tumour microenvironment already influences MUC1 expression in the metastatic disease milieu. Most serum biosensors require an invasive extraction step to make an analysis. Despite their excellent results, biosensors are rare. When biomolecule properties are transferred to a solid substrate, biosensors have a shorter lifetime. The activation mechanism of the HH signalling pathway was studied. GLI is used by NSCLC and SCLC. Lung cancer research use SMO inhibitors. Human and animal lung tumours shrank when treated with SMO inhibitors. In SCLC studies, SMO inhibitors are employed. Oncogenesis of non-small cell lung cancer: HH signalling is involved If this trial succeeds, it may lead to better lung cancer treatments. SMO blockade. Activating GLI transcription factors without using SMO has been discovered. Activation of SMO-independent GLI may produce SMO inhibitor resistance. GLI inhibitors are new GLI research products. Activating the HH pathway and employing GLI inhibitors may help treat cancer. A major emphasis of lung cancer therapy is the discovery of HH pathway inhibitors and GLI-mediated transcriptional regulation. They can be discarded after usage. A different approach is required for flammable materials. The study of the possible carcinogenicity of volatile molecules led to the discovery of several new substances. It is vital to increase tissue collection for routine and companion diagnostic purposes as people become more concerned about their health and seek regular examinations. Existing diagnostic procedures must be evaluated for their strengths and drawbacks, as well as their compatibility. VOCs may be examined any time of day or night. Using an electronic nose instead of a biosensor has several advantages. The sensor is more stable, durable, and reversible. Mass manufacturing is viable. In the absence of theoretical linkages between sensor signals and cancer biology, the amount of data gathered is limited. Electronic noses have been discovered to help a variety of medical ailments, according to a global scientific study.

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