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IDENTIFICATION OF DRUG ANALOGS AS COLORECTAL CANCER INHIBITORS

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Abstract
As a species, humans have a keen awareness of their own well-being and material comforts. Everyone on Earth values their health and wishes they had access to timely medical care for any illness that could threaten it. Today, the illnesses we've been talking about are some of the most widespread in the world. If not caught and treated in time, cancer may spread rapidly, sometimes in a matter of minutes every day.
Cancer is an incurable illness characterized by the unchecked division and development of abnormal cells. Following is an outline of the key points in this article, all of which relate to colon cancer. Where cancer comes from, how it develops, how far it may spread, and what forms it can take are all important questions. Second, the molecular basis of colorectal cancer, including the screening of this disease, along with various treatments, and the role of genomic and chromosomal instability

Keywords: IARC- International Agency of Research on Cancer, ICD-International Classification of Diseases, CL- Colorectal Incidence, ICRCSN- International Colorectal Cancer Screening network, FOBT- Fecaloccult Blood Test, G-FOBT- Guaiac Based test. IMB- Immunological Based Test, CRC- Colorectal Cancer.

1-Introduction

Cancer's molecular foundations have been buried for a long time, but recent research has revealed them, leading to the possibility of novel treatments. Cancer continues to be one of the leading causes of morbidity and mortality despite decades of scientific and clinical research as well as trials of potentially beneficial new treatments. (Ohn et al., 1997).
The mechanism behind the growth of cancer is no longer a secret. In the last twenty years, researchers have made astounding strides in identifying the most fundamental components of the process, which are those that occur on the molecular level. Given that the transmission of new information into clinical practice is a laborious process that is time consuming and costly, no one can accurately anticipate when precisely medicines that are tailored to the molecular abnormalities in cancer cells will find widespread application. However, the amount of effort is now being made.
In point of fact, the word "cancer" may refer to more than one hundred different types of the illness. Nearly major tissue in the human body is capable of giving rise to malignancies, and many tissues may even produce several kinds of tumors. In addition to this, each kind of cancer has its own

particular characteristics. However, the fundamental mechanisms that develop these various cancers seem to have a lot in common with one another.

In a normal and healthy body, there are around 30 trillion cells. These cells live in a sophisticated, interdependent condominium that regulates the growth of one another. In point of fact, normal cells only reproduce when given the signal to do so by several other cells located in close proximity to them.

Proto-oncogenes have the potential to transform into cancer-causing oncogenes, which are responsible for driving excessive cell division. It is possible that the mutations will probably cause the prototype to produce an excessive amount of the growth-stimulatory protein that it encodes or an excessively active variant of that protein.

In contrast, the inactivation of tumor suppressor genes by mutations is a contributing factor in the development of cancer. Because of this, the cell is deprived of vital brakes that prevent it from growing in an uncontrolled manner. The loss of functioning suppressor proteins is the cause of this.

In order for a malignant tumor to form, mutations must first take place in at least six of the founder cell's genes that control its rate of cell division. Alternate forms of additional categories of genes may also play a role in the development of a malignancy by specifically facilitating a proliferating cell to become highly invasive or capable of spreading (rapidly spreading) throughout the body. This is one way in which mutated genes can contribute to the formation of a cancer.

1.1 The Development of a Tumor Takes Place in Stages.

The development of a cancerous tumor in squamous epithelium is represented in the diagram below in a schematic format. Cancers of the epithelial cells, also known as carcinomas, are the most prevalent kind of malignancy. The mass that can be seen here is the product of mutations in four genes, however the percentage of genes that are mutated in actual tumors might vary significantly.

1.2Cell that has been Genetically Altered: When a cell in a normal population (beige) suffers a genetic mutation that enhances its tendency to expand when it would ordinarily rest, this is the beginning of the process that leads to the formation of a tumor.

1) **HYPERPLASIA:**The abnormal cell and its children continue to seem healthy, but they re-produce an excessive amount, a condition known as hyperplasia. After many years, one out of every 100,000 of these cells will eventually experience a second mutation, which will further relax the constraints on cell development.
2) **DYSPLASIA**: The offspring of this cell seem aberrant in form and in orientation; as a result, the tissue is now being said to display dysplasia. This is in addition to the cell's abnormally high rate of proliferation. Once again, after some time has passed, a rare mutation that changes the activity of cells takes place.
3) **ONCOGENES**: Oncogenes are cancer-inducing genes. Although they were first discovered in Viruses, their evolutionary history suggests that normal vertebrate cells include genes whose aberrant expression might contribute to malignant development**.**

2-Infectious Malignant Melanoma.

Melanoma malignant is the kind of the disease that is rising at the fastest rate among Caucasians all over the globe. The rise in cases may be attributed to an increase in sun exposure brought on by changes in clothing preferences and lifestyles that have taken place during the previous fifty years. If not discovered and treated in their early stages, most melanomas develop from preexisting moles in areas of the skin that are exposed to the sun, and they have the potential to quickly spread via the vascular system. The treatment of disseminated illness is inadequate, with the majority of patients succumbing to resistant brain metastases as their cause of death. (Sanchez & Robinson, 1993).

Once upon a time, skin cancers melanoma was thought to be a very uncommon condition. In recent years, there has been a significant rise in the number of cases of malignant melanoma that have been diagnosed in Caucasians all over the globe.

2-Etiology.

Increasing exposure of vulnerable individuals to (UVR) is the primary factor responsible for the current pandemic of malignant melanoma. The most significant contributors to the rise in exposure are changes in lifestyle and patterns of dress. Specifically, individuals are spending more of their free time outside while wearing less clothing because they have more leisure time. Alterations in the atmosphere layer, sunspot activity, and the use of fluorescent lighting are some of the other elements that have been considered as having an influence. The statistics that demonstrate the important role of rising UVR radiation as the dominating factor are strong, despite the fact that they are. Sun-exposed areas are the most common places for malignant melanomas to develop. Studies on populations and migratory patterns have indicated that the mortality rate and incidence of malignant melanoma rise in direct proportion to the quantity of ultraviolet radiation present in different geographic locations. It is not completely understood how being exposed to UVR might result in the development of malignant melanoma. Several hypotheses have been proposed, some of which include the following: direct damage to DNA, the production of harmful radicals, and the inhibition of the immune response. There have been observations of genetic alterations in malignant melanoma cells, including the activation of oncogenes belonging to the Ras family. However, it is yet unknown what function these oncogenes have in the progression of the illness due to the fact that they are present in a wide variety of neoplastic disorders and appear late in the progression of malignant melanoma.

3-Clinical Characteristics:

Malignant melanoma is primarily a disease of upper- and middle-class Caucasian interior employees who have brown or blonde hair, eyes that are not brown, and fair skin, and who spend a significant amount of time outdoors engaging in leisure activities, or who have spent a significant amount of time outdoors engaging in leisure activities. Those who work in technical and executive occupations are the ones who are diagnosed with malignant melanoma the most often, whilst those who work outside have the smallest incidence rate. This latter feature has been seen all throughout the globe and its explanation is still a mystery; nonetheless, it is not merely the product of different ethnic groups working in these different vocational categories. A history of suffering from sunburns several times throughout childhood is another risk factor.

Alterations in color, the formation of an uneven border, and an increase in size are some of the changes that may occur in nevi that are indicators of the advancement of malignant melanoma. The color is the most significant difference. Most of the time, this appears as a deepening of an existing nevus; nevertheless, a variety of color changes may take place, including the formation of hypopigmented regions as well as patches of color that are red or brown. When trying to determine whether or not a border is irregular, magnification of the area may be necessary. An otoscope that has a magnifying head is what we utilize. Recent findings imply that it may not be prudent to wait for an alteration in the size of a nevus just before eliminating it. This is due to the fact that a nevus may experience downward growth before experiencing lateral expansion.

1-Clinical Management:

It is not recommended to do an incisional biopsy unless the lesion is rather significant in size. It is recommended that an excisional biopsy be conducted right up to the fat layer, using a dermal punch or a scalpel, The preventive excision of possibly malignant nevi in high-risk individuals is another option that should be considered. This is especially important if the nevi are located in sun-exposed areas, since this increases the likelihood that they may develop into cancer.

When a histologic diagnosis of malignant melanoma has been established, the primary therapy is an urgent surgical reexcision. According to recent findings, margin widths of one to two centimeters are sufficient for the majority of malignant melanomas and do not contribute to a rise in either regional or systemic recurrence rates. The removal of the muscle fascia below is not suggested anymore, and should not be done just for personal use. Unless there is therapeutic indication of lymph node invasion or as a way of a scientific study, the preventive regional lymph dissection is performed.

4-Cancer's Role in Gene Expression:

It now seems that normal cells may turn malignant and cancer cells can grow more hazardous as a result of a buildup of genetic abnormalities.

Instability of the genetic material is a hallmark of the vast majority of human malignancies and represents among the most active study topics in the field of cancer biology.

Patients afflicted with cancer report having the sensation that an extraterrestrial power has entered their bodies. yet somehow malignancies arise within our own tissue. In point of fact, the weight of information available today suggests that malignancies often originate from a single cell that has undergone a sequence of genetic mutations that cause it to undergo remarkable transformation.

However, the procedure of replication, also known as growth, poses a persistent risk of genetic mutations, which are accidental alterations that have the potential to disrupt the supervisory circuits of a cell. In the event that a single mutation takes place, the newly injured cell, which may seem normally but be somewhat less sensitive to communications from the outside world, may sometimes engage in unscheduled cell division.

An accumulation of genetic damage may, over time, lead a daughter cell to become mostly unresponsive to communications from the outside world and to exhibit characteristics consistent with malignancy. Particularly, it loses its distinguishable form and borders, stops responding to growth-inhibiting signals, and has the capacity to multiply uncontrolled while also causing harm to healthy cells in its vicinity. Worse yet, it has the ability to breach the barriers that keep one organ distinct from another, as well as the capacity to metastasis and develop new colonies in unrelated locations.

The primary reason cells suffer irreversible damage to certain groups of genes is what leads to the development of cancer. In addition to this, it is generating prospects for enhanced diagnosis and treatment. Researchers found many different signals of genetic disorder in tumors when they compared dyed chromosomes from normal cells to those from tumors. This was done so that they could compare the two types of cells.

In cancers, the chromosomes were often damaged, and some of the broken fragments were connected to other chromosomes. In addition to the usual pair, each individual chromosome was found to be present in numerous copies. Other workers, who were convinced that genes were at the core of the problem of cancer, were taking a rather different approach to finding cancer-related genes. These workers were focusing their attention on the genetic makeup of familial malignancies while other researchers were concentrating on the genetic makeup of familial malignancies.

The original copies of the genes that were stolen and then activated are now known as proto-oncogenes. These genes contain instructions that dictate the constituents of proteins that stimulate cell replication. There is a wide variety of these genes that promote healthy development. Some researchers have been able to define the amino acid patterns of receptors, which are proteins that project from the surface of cells and bind to substances known as growth factors. When they are activated by such substances, receptors transmit a signal inside the cell that eventually triggers cells to multiply. A number of the genes include the coding for proteins that are found within the cell and govern the way in which the intracellular growth signal is sent. Still others are responsible for encoding proteins that regulate cell division.

Human cancers, the majority of which are not caused by viruses, may have their origins in mutations that transform helpful proto-oncogenes into oncogenes, which are forms that may cause cancer.

Studies suggested that the transformation of only one copy, or alleles, the expression of these proto-oncogenes was enough to cause certain kinds of cells growing in culture into cancerous cells. This finding is consistent with the hypothesis that was presented before.

They discovered that abnormalities in at least two proto-oncogenes needed to be present, and that malignancy could only be caused by a specific mix of mutations. These results revealed that individual onco-genes, although having the potential to be highly powerful, were not capable of causing tumors by themselves. This was the case despite the fact that they may potentially be quite powerful

5-Cancer-Related Genes in Humans:

The proteins that promote cell division are coded for by genes that are known as proto-oncogenes; the mutant variants of these genes, which are known as oncogenes, may cause the stimulating proteins to be overactive, which in turn causes cells to proliferate in an excessive manner. Proteins that prevent tumor growth are encoded by the genes that act as tumor suppressors. Because mutations may render proteins inactive, they have the potential to deprive cells of the necessary controls that keep them from proliferating uncontrollably. Researchers are still working to figure out the particular roles that many different tumor suppressor genes play in the body. (How Cancer Arises, 1996)

	GENES FOR DEVELOPMENTAL FACTORS AND RECEPTOR.
PDGF	What this gene encodes is platelet-derived growth factor. contributing to glioblastoma (a brain cancer).
erb-B	Encodes the epidermal growth factor receptor. Linked to both breast cancer and glioblastoma, a kind of brain tumour.
erb-B2	This gene encodes a chemokines receptor that goes by many different names. Linked to malignancies of the breast, salivary glands, and ovaries.
RET	Receptor for a growth factor; its DNA code. about thyroid cancer.
	GENES FOR STIMULATORY SIGNAL TRANSDUCTION PATHWAYS RELATED TO CYTOPLASMIC RELAY .
Ki-ras	Linked with cancers of the lung, ovary, colon, and pancreas.
N-ras	Participating in Leukemias.
	TRANSCRIPTION FACTOR GENES THAT ACTIVATE GROWTH-PROMOTIONAL GENES.
C-myc	Correlated with several malignancies, including leukaemias, stomach cancers, lung cancers, and breast cancers.
N-myc	Correlated with glioblastoma and neuroblastoma, two types of brain tumours.
L-myc	Concerned with lung cancer.
	GENES FOR DIFFERENT KINDS OF MOLECULES.
Bcl-2	Encodes a protein that generally prevents cells from killing themselves. part of the process of cutaneous B cell lymphoma.
Bcl-1	Likewise known by the acronym PRAD1, etc. Encodes the proinflammatory element of the cell differentiation clock known as cyclin D1. Participates in malignancies of the breast, head, and neck.
MDM2	Encodes a protein that acts in opposition to the tumour suppressor p53. associated with several diseases, including sarcomas (cancers of the connective tissue).

TRANFORMING GENES

6-The following are some of the major characteristics among cancerous cells growth and normal cell growth:

There are various ways in which cancer cells are distinct from normal ones. for example, cells that cause cancer:

1. Grow despite the lack of any external cues instructing them to do so. The only time normal cells will proliferate is in response to signals like this.
2. Ignore the signals that would ordinarily instruct cells to either cease proliferating or eventually die. Apoptosis (Apoptosis is the term often used to refer to the process of preorganized cell death.)
3. Extend their reach to neighboring regions and then go on to other parts of the body. When normal cells come into contact with other cells, their rate of growth slows down, and normal cells often do not migrate throughout the body.
4. Encourage the growth of blood vessels in the direction of the tumor. These blood arteries provide tumors mostly with O(Oxygen) and N(Nutrients) and eliminate waste products from the tumors. Tumors are supplied with oxygen and nutrition by these blood vessels.
5. In a normal state, the immune system will destroy cells that are damaged or aberrant.

6. To manipulate the body's immune system in a way that helps cancer cells survive and thrive. Some cancer cells, for example, are able to persuade immune cells not to attack the tumor but rather to defend it from harm.
7. Acquire various alterations in their chromosomes, including as redundancy and deletions of chromosomal sections, during the course of their lifetimes. Some cancer cells contain twice as many chromosomes as a healthy cell would normally have.
8. Relies on a different combination of nutrients than regular cells do. In addition, the majority of cancer cells produce power from micronutrients in a manner that is distinct from the majority of normal cell behavior. This encourages the rapid expansion of cancer cells.

7- There are a number of subtypes of cancer, each of which may be classified according to the site where the disease first began to spread and the age at which the first carcinomas appear.

4) SUBTYPES OF CANCER:

- Bladder Cancer.
- Colorectal Cancer.
- Pancreatic Cancer.
- Breast Cancer.
- Lymphoma.
- Kidney (Renal Cell) Cancer.
- Breast Cancer.
- Prostate Cancer.
- Skin Cancer.

5) ALL TYPE CANCER:

- Childhood Cancer.
- A to Z Cancer.
- Metastatic Cancer.
- Recurrent Cancer.
- Adolescent And Young Age Cancer.

8-Various forms of Cancer:

There are over a hundred different kinds of cancer. Cancers are often given their names after the internal organs or tissues in the body where the disease first appeared. For instance, cancer of the lungs begins in the lungs, but cancer of the brain begins in the brain. Cancers may also be classified according to the kinds of cells from which they originated, such as epithelial cells or squamous cells, for example. Colon Cancer Treatment (PDQ®)–Patient Version. (2022, April 6). National Cancer Institute. Retrieved January 14, 2023, from https://www.cancer.gov/types/colorectal/patient/colon-treatment-pdq.

You may search the NCI's website for data on particular forms of cancer depending on the location of the cancer in the body, or you can use our A-to-Z shortlist of Cancers to get the information you need. We additionally have information about malignancies that occur in children as well as cancers that occur in teenagers and young adults.

The following is a list of several categories of malignancies that start in certain kinds of cells:

1-Carcinoma: The most prevalent kind of cancer is known as a carcinoma. Epithelial cells, and which are the are the body cells that coat the interior and exterior surfaces of the body, are the cells that are responsible for their formation. When examined via a microscope, epithelial cells often take on the appearance of columns. There are many different kinds of epithelial cells.

Specific names have been given to cancers that originate in the many kinds of epithelial cells:

The cancer known as adenocarcinoma develops in Decidua that are responsible for the production of fluids or mucus. When a certain kind of epithelial cell is found in a tissue, that tissue may be said to be glandular. Adenocarcinomas make up the vast majority of malignancies that occur in the female

breast, colon, and prostate. Cancer that begins in the lowest or bottom (base) epidermis of the skin, which is the topmost epidermis on a person 's body, is called basal cell carcinoma. This kind of cancer is the most common form of skin cancer.

2-Sarcoma: Sarcomas are a kind of cancer that may develop in bone as well as soft tissues which would include muscles, fat, arteries, lymphatic vessels, and fibrous tissue. Sarcomas can also spread to other organs.
The most prevalent kind of bone cancer is called osteosarcoma.

3-Leukemia: Leukemias are a group of cancers that arise in the human blood tissues of the bone marrow. These types of cancer do not result in the formation of solid tumors. Instead, an abnormally high number of white blood cells known as leukemia cells and Cancer of the Blood blast cells accumulate in the bloodstream and bone marrow, which causes normal blood cells to get squished and die off. When there are fewer regular blood cells in the body, it is more difficult for the body to provide O(OXYGEN)t hen there are fewer regular blood cells in the body.

4-Lymphoma: Lymphoma, sometimes known as lymphoma, is a kind of cancer that starts in white blood cells. These white blood cells help the immune system fight off illness and are a regulation of the immunologic system. Lymphomas are characterized by the accumulation of aberrant lymphocytes in various organs of the body, including the fluid nodes and lymph arteries.

8.1-There are two primary subtypes of lymphoma, which are as follows:
Reed-Sternberg cells are aberrant lymphocytes, and people who have Hodgkin lymphoma have them in their bodies. In most cases, these cells originate from B cells.
Cancers that originate in lymphocytes are categorized into a wide category known as non-Hodgkin lymphomas. Both B cells and T cells may give rise to cancer, and either kind can progress swiftly or slowly.
Melanoma is a kind of cancer that develops in cells that have the potential to become melanocytes, which are specialized cells that are responsible for the production of melanin content. The vast majority of melanomas begin as growths on the skin, but the disease may also manifest itself in other highly pigmented tissues, including the eye.

9-Differences in colorectal cancer diagnoses across the world:
There are considerable differences in the prevalence of colorectal cancer among countries, with some countries having far higher rates of the disease than others. Colorectal cancer ranks as the fourth most frequent carcinoma in men and the 3rd most frequent cancer in women globally. Some of the health conditions for (CRC) include being overweight, eating a diet that is inadequate in fruitage Along with Greenery, being physically inactive, and smoking, and as a result, this disease was once seen primarily in long-established developed nations whose communities generally exhibit these factors. 7However, in current years it has come to light that newly developed nations all over the world, where the risk of colorectal cancer used to be lower, are now experiencing high rates of the disease. The purposes of this article are to provide information regarding colorectal cancer screening initiatives all over the world and to describe the global patterns of colorectal cancer mortality rates based on the most recent data that is available from (IARC).

10-Data resources and research methodologies:
Worldwide, population-based cancer registries gather data on the incidence of cancer. These registries might include national populations or, more typically, regions within countries.

6) The International Agency for Research on Cancer has collated and made this cancer incidence statistics available in quantities I to IX of (CI5).
7) The most current capacity of CI5 (volume IX) comprises information over 225 sex offender registries in 60 countries and represents roughly 11percent of the world population.

8) There are nine aggregated, cross-sectional rates of colorectal cancer incidence for the years 1998–2002 for several registries.
9) Many nations have various registers incorporated among 2 registrations for each nation: the ones having consequently increased along with those one which consequently decreased.
10) (CRC) incidence data were categorized in accordance with the Tenth edition (ICD-O), (C18–C21) economically de-eloped nations and certain economically transitioning countries.

The quality of mortality statistics varies by country, with a high accuracy of primary cause of death indicated in longstanding, financially developed countries and a lesser accuracy reported in recently developed or economically transitional countries.
Data on deaths from colorectal cancer were classified according to the version of the ICD that was present at the time of the patients' deaths.
Carcinoma of the anus is not commonly combined with Colorectal malignancies in US cancer statistics, and yet is combined in global cancer statis-tics along with Anal Cancer is uncommon.
A literature study served as the primary source for the above information on worldwide colorectal cancer screening efforts. The vast bulk of the data came from the (ICRCSN), and were acquired via a paper that was written and published by Benson et al.14.

11-The prevalence of colorectal cancer:
Incidences per 100,000 among boys in the timespan of 1998–2002 reported to vary from 4.1 in District (Kollam) Kerala to 59.1 in Country Central Europe. Male mortality rates varied from 3.6% in District (Kollam) Kerala to 39.5% in New Zealand. Colorectal cancer incidence rates were found to be greatest in registries from Mainland Europe, Latin America, and Oceania. In contrast, registries in Asia, Central Africa, and Latin America reported the lowest rates.
Incidence rates of colorectal cancer among men (1998-2002) in the Country Central Europe, Tokyo, and Czech Slovakia (Fig.1) have surpassed those of long-established, industrialized countries like New Zealand, Canberra, and the U.S.A, which had previously reported the highest incidence rates globally.
The high prevalence of obesity associated with "Westernization," including the consumption of high-calorie-dense foods and physical inactivity, is likely to blame for the high rates of colorectal cancer in newly developed or economically transitioning countries like the Czech Republic, Slovakia, and some others in Eastern Europe.
While most of the greatest rates of colorectal cancer in men were documented in Europe, Latin America, and Oceania, several registries in Asia also found very greater incidence in Japan, Singapore, and Israel. These three nations have seen a rise in colorectal cancer rates in recent years, and the cause is likely related to changes in the local environment or people's habits.
In Japan, a developed nation along with the strongest economies globally, the high prevalence of colorectal cancer, especially among men, is most likely attributable to alterations in food consumption.
New Zealand, Australia (Tasmania), and Israel had the greatest (CRC) incidence rates among women (Fig. 1). Colorectal cancer has historically high incidence rates in New Zealand and Australia, as well as many other long-standing developed countries in Europe and Washington, D.C. This is likely the outcome of habits linked with urbanization.

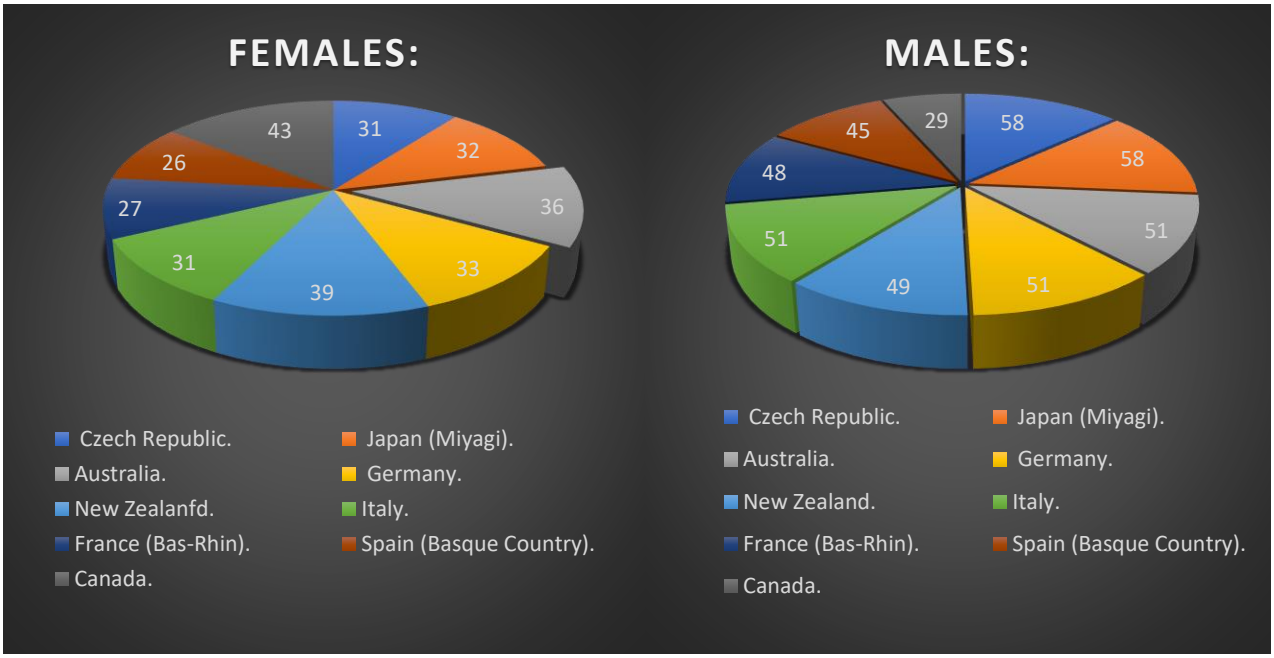

Figure1: Registries with the Greatest age range Colorectal Cancer Incidence Rates, Broken Down by Gender,1998–2002 (NPCR) UK refers to the United Kingdom; USA and NPCR both refer to the United States of America. Cancer Incidence Across the Five Continents9 is the source for this information

Figure1.2: Registries with the Greatest age range Colorectal Cancer Incidence Rates, Broken Down by Gender, 1998–2002 (NPCR) UK refers to the United Kingdom; USA and NPCR both refer to the United States of America. Cancer Incidence Across the Five Continents9 is the source for this information.

Table1: Death Rates from Colorectal Cancer, Age-Adjusted and by Gender, Selected Countries, 2005* (WHO Mortality Database).

MALE			FEMALE		
RANK	COUNTRY	RANGE	RANK	COUNTRY	RANGE
1	Slovakia	30.8	1	Slovakia	15.3
2	Czech Republic	30.0	2	Czech Republic	14.1
4	Croatia	25.0	4	Croatia	13.4
5	Slovenia	21.0	5	Slovenia	12.7
6	Estonia	20.2	6	Estonia	12.0
7	Russia	19.4	7	Russia	11.8
8	Latvia	19.2	8	Latvia	11.7
9	New Zealand	18.3	9	New Zealand	10.9
10	Ireland	17.7	10	Ireland	10.6
11	Spain	17.5	11	Spain	10.6
12	Germany	16.9	12	Germany	10.5
13	China (Hong Kong)	16.8	13	China (Hong Kong)	10.2
14	Australia	16.3	14	Australia	9.9
15	Japan	15.8	15	Japan	9.6
16	Romania	15.6	16	Romania	9.6
17	Australia	15.2	17	Australia	9.2
18	France	14.8	18	France	9.1
19	UK	14.8	19	UK	9.0
20	Canada	14.8	20	Canada	9.0
21	Israel	14.5	21	Israel	8.7
22	Korea	12.7	22	Korea	8.5
23	Singapore	12.6	23	Singapore	8.1
24	Kazakhstan	12.1	24	Kazakhstan	7.5
25	US	11.9	25	US	6.8
26	Chile	8.4	26	Chile	5.6
27	South Africa	7.7	27	South Africa	4.5
28	Brazil	5.9	28	Brazil	3.5
29	Mexico	4.0	29	Mexico	3.4
30	Ecuador	3.4	30	Ecuador	10.4

Incidence rates of colorectal cancer among women have decreased in New Zealand and steadied in Australia (Tasmania), but have risen steadily in Israel in recent years.
Throughout these and other registers, the average age of women is much lower than that of men. Females have been shown to have lower incidences of colorectal cancer, and this disparity may be attributable to variations in risk behaviors like smoking.
The lowest rates of colon cancer incidence were found in registries in India (Nagpur, Puna, and Karunagappally), Oman, Tanta, Algeria (Setif), and Islamabad (South Karachi), and this was true for both men and women. Low colorectal cancer rates may be a result of a lack of exposure to carcinogens in these poor countries.

12-Mortality rate from colorectal cancer:

However, death trends for colorectal cancer have also declined in certain Asian and Eastern European. nations, despite the fact that these countries have incidence rates that are among the highest in the world. In Japan, the mortality rate for males fell by 0.9% annually between the years 1996 and 2005, whereas the death rate for women rose by 5.0% annually between the years 1992 and 2005. In the same vein, mortality rates in the Czech Republic, which had the second highest rates in 2005 across overall in males and females (Table4), declined by 1.0percentage points per year from 1994 until 2005 for men, and by 1.2% annually from 1988 to 2005 for women.
There is a possibility that the rising death rates in these nations are a mirror of the rising colorectal cancer incidence rates that have been reported in economically transitioning nations all over the globe.

13-Preventative Testing for Colorectal Cancer:

Consequently, screening decreases the death rate associated with colon cancer over the course of time by lowering the incidence of the disease and/or by finding cancers at earlier stages, when they have a better prognosis. In point of fact, the recent drop in colorectal carcinoma incidence in the United States has been attributed in large part to the increasing use of screening, which has been identified to be one of the most significant reasons responsible for the fall.
Although colonoscopy is sometimes referred to as the "gold standard" for screening for colon cancer, it is more expensive, takes more preparation on the part of the examiner, and offers the patient less benefits in terms of convenience.
Because of this, a population-based colon cancer screening program that relies on colonoscopy is more difficult, requires more resources, and is less realistic in most countries. Furthermore, it is not at all practical in countries with little resources. The fecal occult blood test, often known as the (FOBT), is an alternative for colorectal cancer screening that is more practicable in many parts of the globe. This test is less sensitive than structural inspections; however, it is also less costly and requires less effort to carry out.
Current screening recommendations in the United States for the identification of malignant tumors polyps and colon malignancy in seniors with average risk (those aged 50 years and older) encompass annual stool testing to a slightly elevated guaiac- or immunobead test (G-IMBT), relatively frequent faecal DNA testing, flexible sigmoidoscopy periodically five years, laparoscopy every 10 years, dual barium almost in every Five years, or computed colonography every five years. Other.
It is suggested to do FOBTs on a yearly basis, including both guaiac-based tests (G-FOBT) and faecal immunochemical assays (FIT). Although gFOBT, the stool blood test that is most often performed, has been proven to cut the risk of dying from colorectal cancer by up to 33 percent. It is not as sensitive as structural investigations and has a lower rate of success in preventing colorectal cancer.
It was reported that Italy has the highest number of research and programmes, with 8 currently active that employed different combinations of flexible sigmoidoscopy, FOBT, and colonoscopy.
The ICRCSN was founded in 2003 and has compiled a list of structured screening initiatives and pilot studies that were started before 2004.
The faecal occult blood test (FOBT) is used in the majority of nations that have national screening programmes in place (the Country in Central Europe, Israel, and Japan), while carcinoma screening with colonoscopy has just recently been implemented in Poland and Germany.

In addition, a metric known as the (HEDIS) can assist employers in evaluating the performance of health plans with regard to colorectal cancer screening. This metric is broadly viewed as a stimulus for health plans to increase the number of people who undergo colorectal cancer screening.
In contrast, the majority of Asian nations provide very little assistance from the government for colorectal cancer screening and do not have any form of colon cancer screening strategy, including screening recommendations (eg, Bandar Seri Begawan, Beijing, India, Jakarta, Kuala Lumpur, the Manila, Bangkok, and Hanoi).
However, because mortality rates from colorectal cancer are rising in a number of economically developing countries, in particular in nations that are adjusting to Western ways of life or that have populations that are getting older, there is likely to be an increase in the consideration of incorporating targeted screening for colon cancer over the course of time.
This may have been a factor in the rise in colorectal cancer incidence rates that were seen in Japanese databases in the middle to late 1990s after Japan included FOBT-based colorectal cancer screening as part of its public health program in 1992.
However, rises in death rates are still happening in nations that may have more constricted resources, such as Mexico and Brazil in Latin America and Serbia and Moscow in Romania, in comparison with long-standing, financially developed nations. These countries include Mexico City and Brazil in South And central America and Romania and Moscow in Eastern Europe. The most likely reason for the decline in mortality rates associated with colorectal cancer is carcinoma screening and/or improvements in treatment.
If these behaviors are not changed, it is likely that they will continue to contribute to the growing global colorectal cancer burden. This can be attributed to the expanding incidence of obesity and the decreasing levels of physiological behavior in numerous parts of the world as a result of "Westernization."
The incidence of colorectal cancer is expected to rise, making it an even more significant threat to public health throughout the globe. Screening for colorectal cancer has been shown to significantly lower the risk of death from the illness and, in some cases, may even prevent the disease from developing by removing potentially malignant polyps.

14-Blood or an alteration in bowel movements are symptoms of colon cancer.
Colon cancer, among other illnesses, may induce these symptoms.

- Alteration in bowel routine.
- Visible or trace amounts of blood in the faeces.
- Abnormal bowel movements, such as diarrhea, constipation, or the sensation that the bowels are not emptying completely.
- Narrower than typical stools.
- cramping, fullness, and bloating that persist or recur often.
- Loss of weight with no apparent cause.
- My body is telling me that it's time for bed.
- Vomiting.

15-The rectal and colonic areas are examined during diagnostic testing for colon cancer.
Some of the following diagnostic tools and techniques might be employed:
1. Assessment of present health and past medical history: -Checking for abnormalities or symptoms of illness during a general examination of the body is part of a comprehensive physiological exam and health history. The patient's medical history will also be recorded, including any ailments they've had and the treatments they've received.
Digital rectal examination: -Using a digital probe, a doctor examines the rectum. A greased, gloved finger is inserted into the rectum by the physician or nurse to check for lumps or other abnormalities.
The faeces occult blood test (FOBT): is a diagnostic procedure used to detect the presence of blood in faeces (solid waste) by use of a microscopic examination. Returning a stool sample to the physician or lab for analysis involves collecting a little amount on a designated cards or in a suitable container.

The presence of blood in the faeces may indicate the presence of adenoma, cancer, or other diseases. Colon Cancer Treatment (PDQ®)–Patient Version. (2022, April 6). National Cancer Institute. Retrieved January 14, 2023, from https://www.cancer.gov/types/colorectal/patient/colon-treatment-pdq.

One may choose from two distinct varieties of FOBTs:

- **(G_FOBT)**: -With the Guaiac FOBT, a chemical is used to analyze the faeces sample on the designated card. The unique card will switch colors to indicate the presence of blood in the stool.
- **An immunochemical FOBT**: - involves the addition of a liquid to the feces sample. A machine equipped with autoantibodies that can identify blood in the faeces is then injected with this concoction. A line will show in the machine's display if there is bleeding in the faeces. Fecal immunochemical test (FIT) is another name for this analysis.

2. Sigmoidoscopy: - is a diagnostic technique used to examine the lower colon, including the sigmoid section, for polyps (bubbling tissue), other abnormal regions, and cancer. The sigmoid colon is reached by using a sigmoidoscope via the rectum. A slender, tube-shaped device containing a light and a viewing lens, a sigmoidoscope is used to examine the sigmoid colon. In certain cases, it may be used to extract abnormal cells or tissue samples that can then be examined for cancerous changes under a microscope.

3. Colonoscopy: -is a diagnostic technique used to inspect the colon and rectum for precancerous polyps or cancerous growths. An endoscope is sent via the rectum and into the colon. Colonoscopies are performed using a slender, tube-shaped equipment equipped with a Laser lamp and a lens. Adenomas or tissue samples may be removed and examined for malignancy with this device.

4. Computed tomography x-rays: - are used to provide a sequence of images of the colon, simulating a colonoscopy. The images are stitched together by a computer to provide clear representations of the colons inside that may reveal polyps and other abnormalities. Colonography and computed tomography colonography are other names for this examination.

5. BIOPSY: -The term "biopsy" refers to the process of removing cellular or tissues so that a pathologist may examine them under a microscope for symptoms of malignancy.

6. DNA STOOL TEST EXAMINATION: -The DNA stool test is a screening for colorectal cancer that analyses DNA from stool cells.

16-Colorectal cancer inhibitors identified in drug analogs:

Chemoprevention-curcumin analogue 1.1 (CCA-1.1) is a Pentagamavunone-1 (PGV-1) derivative with enhanced chemical and physical features. Using bioinformatics, this work looks into the possible therapeutic targets and mechanisms of CCA-1.1 for colorectal cancer treatment. Mutations in genes linked to

The cBioPortal accessible database was used to obtain information on colon cancer. CCA-1.1 target genes were found in seven online databases. The possible target genes' genome ontological profiles, KEGG-related pathways, protein-protein interaction (PPI) networks, linked illnesses, and medication connections were then examined. A total of 914 altered genes and 812 prediction target genes of CCA-1.1 were aligned, yielding 93 genes of matches, most of which were concentrated in oncogenesis and EGFR tyrosine-kinase inhibitor resistance pathways. The top 20 hub genes were shown to be heavily involved with colorectal cancer.

Despite the fact that large-scale research has been conducted to find the relevant biomarkers and mechanisms of colon cancer, we were always lost in the intensive clinical application. Considering drug-target prediction databases, it will provide additional information from which to acquire. associated diagnostic biomarker and pathways in colon cancer, as well as the discovery of new

pharmacological markers with high prognostic importance. The medicine of choice in colon cancer treatment is 5-fluorouracil (5-FU), which is often used as the foundation of regimented regimens including such as FOLFIRI (5-FU, leucovorin, and irinotecan) and FOLFOX (5-FU, leucovorin, and irinotecan) (oxaliplatin, leucovorin, levo-leucovorin, and 5-FU) To improve effectiveness, a combination of various targeted treatments, such like cetuximab, panitu mumab, and bevacizumab, is often employed.

- **Data gathering and processing:**

CCA-1.1's structure was developed using CCA-1.1's SMILES: CC1 = CC(C=C2/CC(=C/CC3) = CC(C) = C(O)C(C) = C3)C2O) = CC(C) = C1O. The target genes of CCA-1.1 predicted from seven internet databases were acquired using the default settings of Swiss Target Prediction Hit Pick SEA Search, MoltarPRed, TargetNet, BindingDB, and DINIES. We then combined and consolidated the findings to determine the overall number of target genes. We utilised interactivenn, an online tool for creating Venn diagrams, to assemble target sequences from all databases without duplication.
The altered genes in colon cancer were gathered from 139 colon cancer samples, including 29 colorectal adenoma cases (Case CCC, PNAS 2015) and 110 colorectal cancer samples (CPTAC-2 Prospective, Cell 2019), using the cBioPortal database. Data were obtained and analysed using Word And excel 2013 and only mutations in "cancer" genes were selected.

- **Analysis of gene ontology and Pathway enrichment:**

CCA-1.1 gene products were screened utilising biochemical pathway, biological process, cellular component, and KEGG pathway analysis. DAVID v6.8 is the Database for Identification, Visualization, and Integrated Discovery. We used a P-value of 0.05 to apply the cut-off value. The enrichment of the KEGG pathway with bar chart display was also shown utilising the ORA, Web Gestalt, with a false discovery rate (FDR) level of 0.05.

- **Predictive biomarker protein-protein interaction network and hub gene building:**

We created a protein-protein interaction (PPI) network map using STRING-DB v11.0. The cut-off parameters were a reliability rating of > 0.4 and a total amount of interactors of =0. Using a degree cut-off of 2, a node score cut-off of 0.2, a k-core of 2, and a maximum depth of 100, the Molecular Complex Recognition component of Cytoscape was used to reveal the biological importance of genetic modules in colon cancer. Furthermore, 20 hub genes were chosen using cyto Hubba plugins with a confidence score greater than 0.4 and a total amount of interactors greater than 5.

- **Analyses of gene-related diseases and medication interactions:**

We next explored the (a) to discover possible locations of CCA-1.1 and give comprehensive insight into the linkages in medication targets and processes with numerous licenced pharmaceuticals used during colon cancer treatment (b) Fig. 1. (a) CCA-1.1, also known as 2,5-bis-(4-hydroxy-3,5-dimethylbenzylidene)-cyclopentanol, and (b) PGV-1, also known as 2,5-bis-(4-hydroxy-3,5-dimethylbenzylidene)-cyclopentanone. F. Wulandari and co. Reports on Genes the ORA from the Web Gestalt revealed 21 gene-related illness and medication connections of the top 20 target genes (FDR 0.05). The gene-related illness was discovered using the OMIM parameter, whereas the medication connections were discovered using the GLAD4U parameter.

- **Building a PPI network and selecting a hub gene:**

STRINGDB assesses the network connection between genes in order to thoroughly unearth the target sequences of colon cancer. From a total of 93 genes built to the PPI network complex, we discovered 93 nodes and 1138 edges with an overall node degree of 24.5, an average city clumping coefficients of 0.616, and a PPI enriched P value of 1.0e16. The cytoHubba plugin was then used. (Confidence score > 0.4 and total amount of interactors > 5) to identify the top twenty target genes with the highest degree score, which include TP53, AKT1, EGFR, SRC, HSP90AA1, ALB, IGF1, ESR1, MAPK1, ERBB2, JAK2, MDM2, FYN, CDC42, PTPRC, AR, KDR, MAP2K1, HSP90AB1, and PLCG1.

16.1-It is important to determine whether the disease has spread inside the colon or elsewhere in the body after a diagnosis of colon cancer.

Staging is the method used to determine whether colon cancer has spread locally or to other areas of the body. The progression of an illness is measured in terms of the data obtained throughout the staging procedure. It is vital to understand the phase in order to organize therapy.

In the staging process, the essential tests and processes may be used:

1. **A computed tomography (CT) scan or (CAT scan)**: is a diagnostic imaging technique used to provide cross-sectional and anatomically precise images of anatomical structures deep inside the human body, most often the belly, pelvis, and chest. An x-ray machine and a computer work together to create the images. To make the internal organs or tissues more visible, a dye is either infused into a vein or ingested. Computed tomography, computerized tomography, and computerized axial tomography are various names for the same process.

2. **Magnetic resonance imaging (MRI):** Technique that takes many high-resolution images of the interior of the body, in this case the colon, using a powerful electromagnet, radio waves wavelength, and a computer. The patient receives a gadolinium-based material through intravenous injection. The cancer cells are highlighted in the scan because gadolinium accumulates around them. The term "nuclear magnetic resonance imaging" may also be used to describe this method (NMRI).

3. **Positron emission tomography (PET): -** Scans are used to locate cancerous tumor cells in the human body. Sugar (glucose) that has been irradiated is administered intravenously. The PET scanner may provide an image of the body's glucose use by revolving around it. Since malignant tumor cells are more metabolically active and consume glucose at a higher rate than healthy cells, they appear more vividly in the image.

An x-ray showing the inside structures of the chest, sometimes known as a "chest x-ray." An image of the interior of the body may be taken using an x-ray, which is a form of radiation beam that can pass across the Human body and onto film.

Operation: Surgical excision and examination of the colon for evidence of tumor metastasis.

Performing a lymph node biopsy entail taking out a lymph node (or a portion of one). Under the microscope, a pathologist examines the lymphatic node tissue for signs of malignancy.

17-Conclusion:

Cancer is one of the leading causes of morbidity and mortality despite decades of scientific and clinical research. In the last twenty years, researchers have made astounding strides in identifying the most fundamental components of the disease. No one can accurately anticipate when precisely medicines that are tailored to the molecular abnormalities in cancer cells will find widespread application. Proto-oncogenes are cells that have the potential to transform into cancer-causing oncogenes, which are responsible for driving excessive cell division. Inactivation of tumor suppressor genes by mutations is a contributing factor in the development of cancer.

Mutations must take place in at least six of the founder cell's genes that control its rate of cell division before a malignant tumor can form. The development of a cancerous tumor in squamous epithelium is represented in the diagram below in a schematic format. Cancers of the epithelial cells, also known as carcinomas, are the most prevalent kind of malignancy. One out of every 100,000 of these cells will eventually experience a second mutation, which will further relax the constraints on cell development. Melanoma malignant is the kind of the disease that is rising at the fastest rate among Caucasians all over the globe.

The most significant contributors to the rise in exposure are changes in lifestyle and patterns of dress. If not discovered and treated in their early stages, most melanomas develop from preexisting moles in areas of the skin that are exposed to the sun. The mortality rate and incidence of malignant melanoma rise in direct proportion to the quantity of ultraviolet radiation present in different geographic locations. Individuals are spending more of their free time outside while wearing less

clothing because they have more leisure time. Alterations in the atmosphere layer, sunspot activity, and the use of fluorescent lighting are some of the other elements that have been considered.
Malignant melanoma is primarily a disease of upper- and middle-class Caucasian interior employees who have brown or blonde hair, eyes that are not brown, and fair skin. A history of suffering from sunburns several times throughout childhood is another risk factor. Alterations in color, the formation of an uneven border, and an increase in size are some of the changes that may occur in nevi. It is recommended that an excisional biopsy be conducted right up to the fat layer, using a dermal punch or a scalpel. The preventive excision of possibly malignant nevi in high-risk individuals is another option that should be considered.
According to recent findings, margin widths of one to two centimeters are sufficient for the majority of malignant melanomas. Instability of the genetic material is a hallmark of the vast majority of human malignancies and represents among the most active study topics in the field of cancer biology. In cancers, the chromosomes were often damaged, and some of the broken fragments were connected to other chromosomes. Researchers found many different signals of genetic disorder in tumors when they compared chromosomes from normal cells to those from tumors.

17-Declaration of Competing Interest:
The Authors Declare no Conflict of Interest.

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