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Review Article

ENVIRONMENTAL AND ANTHROPOGENIC CARCINOGENS AND THEIR CARCINOGENIC EFFECTS ON HUMANS

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ABSTRACT

The review describes the environmental and anthropogenic carcinogens and their carcinogenicity. Environmental and anthropogenic carcinogens can be chemicals (exposed from chemical industries, alcoholic beverages, welding and wood dust, *etc*.), radiations (UV-rays, X-rays, γ-rays, radon, neutron, thorium, *etc*.), microbiological agents (viruses and bacterial infections), and natural products (tobacco, nicotine, areca nut, yerba mate, safrole, cycasin, *etc*.). Diet related factors (heterocyclic amines, saccharine, cyclamate, *etc*.) are through to account for about 30-35% of cancers in developing and developed countries. Obesity may raise incidence of cancer in the oesophagus, breast, colorectum, endometrium, and kidney.

Key words: Carcinogens, environmental and anthropogenic carcinogens, chemotherapy, harmone therapy.

Abbreviations: International Agency for Research on Cancer (IARC), Polycyclic Aromatic Hydrocarbons (PAH), 2-Amino-3-methylimidazo[4,5-f]quinoline (IQ) 2-Amino-3,4-dimethylimidazo[4,5-f]quinoline (MeIQ), 2-Amino-1-methyl-6-phenylimiazo[4,5-b]pyridine (PhIP), 2-Amino3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx).

INTRODUCTION:

The origin of the word cancer is given by the Greek physician **Hippocrates** (460-370 BC), who is known as the **"Father of Medicine".** The study of cancer called oncology (Greek word Oncos means Tumor). Cancer discoveries in anatomy, physiology, chemistry, epidemiology, and other related fields made oncology. Technological advances and the ever increasing understanding of cancer make this field one of the most important research areas of modern medicine. Cancer is not one disease but many disorders that shares profound growth irregularities. Some cancers, such as Hodgkin lymphoma, acute leukaemia and other cancer of skin, prostate, colorectal, breast, lung, *etc*. are curable but the curability of these cancer depends on caught at on early stage (1-3) whereas others cancers (*e.g.* pancreatic adenocarcinoma, *etc*.) are not curable and have high mortality rate. Learning more about its cause and pathogenesis is only hope for controlling cancer.

Environmental, biological and occupational causes of cancer:

The list of environmental, biological, and occupational factors that can influence the development of cancer is diverse, particularly when we consider these carcinogenic factors in its broadest sense. Potential carcinogens can be present in diets (*e.g.* artificial sweetners, meat *etc.*), alcohol, tobacco smoke, yerba mate, areca nut, workplace, home environments, outdoor air, soil, water, sunlight, infections from viruses and bacteria [*e.g.* Hepatitis-B virus (liver carcinoma), Epstein Barr virus (Burkitt's lymphoma and Hodgkin's disease), HHV8 and HIV (Kaposi's sarcoma), Human immunodeficiency virus (many sites), the bacterium *Helicobacter pylori* (stomach) *etc*.], some medical therapies, hormones, and inherited factors can also influence the development of cancer (5-6).

Based on various observations, it concluded that tobacco is a contributor in approximately 30% of all cancer deaths in developed countries. In addition, tobacco smoking causes even more deaths from respiratory, vascular, and other diseases than from cancer, so that, in total, tobacco smoking is estimated to account for approximately 4-5 million deaths a year worldwide. This death parameter is projected to increase to approximately 10 million a year by 2030, if current tobacco smoking patterns are continue (7). One third of cancers caused by lifestyle factors, including dietary factors cause 35% of all cancers, infections 10%, occupational exposures 8%, natural sources of ionizing radiation 2%, chemical pollution 2%, and others 5%[8] which are summarized in Fig. 1.

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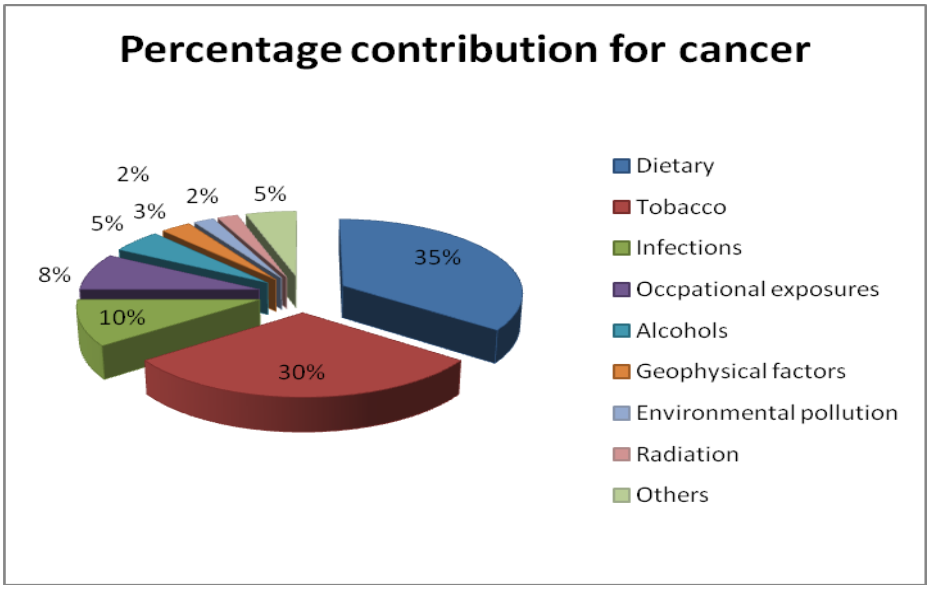


Figure 1: Pi representations of main contributions for cancer [8]

Chemical carcinogens:

Carcinogenesis due to exogenous chemicals:

We recognize majority of initiating chemicals are mutagenic in nature and they act as human carcinogens. A large number of chemicals are classified as possible human carcinogens in (Tables 1). It has been estimated that exposures to environmental chemical may contribute significantly to the causation of human cancers, when exposures are related to "life-style" as (3-4 & 9-33):

Carcinogenic Chemicals+ DNA = DNA Adduct → Mutation

Carcinogenesis due to alcoholic beverages:

The main constructive components of all alcoholic beverages are ethanol and water. Alcoholic beverages also have volatile and non-volatile flavour compounds that originate from raw materials by fermentation and maturation, synthetic substances added to specially flavored beverages. Some of these components and contaminants identified as "known or suspected human carcinogen" including nitrosamines, acetaldehyde, asbestos, aflatoxins, ethyl carbamate (urethane), and arsenic compounds (34).

High consumption of alcoholic beverages increased frequencies of chromosomal aberrations, sister chromatid exchange, and aneuploidy were found in the peripheral blood lymphocytes of alcoholics. Ethanol free extracts of some alcoholic beverages caused mutations in bacteria and sister chromatid exchange in cultured human cells. And other effects are reduced power of immune system, quality of life, cardiovascular disease, diabetes, overweight and obesity, risks to unborn babies, liver diseases, mental health conditions, tolerance, dependence, long-term cognitive impairment, self-harm, nutrition-related conditions, cancer (*e.g.*, cancer of the mouth, pharynx, larynx, esophagus, liver, colorectum, and female breast). The risk of cancer increases with increasing consumption level of alcoholic beverages (35).

Carcinogenesis due to welding and allied processes:

Fume exposed during welding is comprised of solid particles, usually less than 1.0µm in size, formed by oxidation and condensation of the vaporized metals. These particles are capable of being deposited in the lungs. The chemical composition of the welding exposures (fumes and gases) depends on welded material, process, composition of the welding electrode, work environment, including the location (indoor v/s outdoor), ventilation, degree of enclosure of the work station, length of exposure, and personal protection equipment. Most common welding exposures are fumes and gases (Cadmium oxide, chromium (VI), copper, iron oxide, magnesium oxide, manganese, nickel, zinc oxide, fumes, ozone, nitrogen oxide, carbon monoxide, *etc.*), radiation (visible, *X*-rays and infrared radiations).

Welding exposure can cause respiratory irritation, siderosis, metal fume fever, nervous system disorders, irritation of respiratory system, eye, nose and throat irritation, chest pain, kidney damage, fluid in the lungs, fluorides, haemorrhage, dermatitis, eczema, bone and joint problems, headaches, dizziness and related effects, chronic effects of welding fumes and gases are Prostate and lung cancer (Cadmium or Cadmium Oxides), lung cancer [Chromium (VI)], nose, larynx, and lung cancer (nickel) (36-37).

Table 1. Exogenous chemicals classified as established human carcinogens

Agents or groups of agents	Human cancer site for which reasonable evidence is available	Occupation or industry in which the substance found
Aflatoxin	Liver cancer	Feed production industry, workers loading and unloading cargo, aflatoxins present in a wide range of food commodities, pistachios, dried fruit, figs, and dairy products.
Asbestos	Malignant lung cancer, mesothelioma, and asbestosis	Mining, product manufacture, insulation, shipyard workers, sheet-metal workers, asbestos, cement industry.
Arsenic and arsenic containing compounds	Lung, skin, liver cancer (angiosarcoma)	Glass, metals, non-ferrous metal smelting, production and packing of pesticides, sheep dip manufacture, wool fibre production, mining of ores containing arsenic.
Cadmium and cadmium containing compounds	Lung, pancreatic, breast and bladder cancer	Diet, smoking, cadmium smelter workers, battery production workers, cadmium-copper alloy workers, dyes and pigments production, electroplating process.
Benzidine	Urinary-bladder and pancreatic cancer	Dye stuffs, pigment manufacture, waste water and sludges.
Bis (chloromethyl) ether and chloromethyl methyl ether	Lung cancer	Plastic and rubber production industry, chemical intermediate, alkylating agent, laboratory reagent, plastic manufacturing, ion-exchange resins and polymers.
Erionite	Mesothelioma, lung cancer	Erionite mining and production, zeolite mine, waste treatment, sewage, agricultural waste, cement aggregates, building materials, volcanic ash.
Chromium hexavalent compounds	Lung and sinonasal cavity cancer	Chromate production plants, dyes, pigments, plating, engraving, chromium ferro-alloy production, stainless-steel welding, wood preservatives, leather tanning, inks, photography, lithography, food.
Coal-tars and pitches	Skin, lung, kidney and bladder cancer	Production of refined chemicals, coal-tar products (patent fuel), electrodes, coke production, coal gasification, aluminium production, foundries, road paving and construction.
Ethylene oxide	Leukemia and stomach cancer	Chemical industry, sterilizing agent (hospitals, spice fumigation).
Formaldehyde	Specifically myeloid leukemia, nasopharyngeal, sinonasal, and lymphohematopoietic cancer	Production of formaldehyde, pathologists, medical laboratory, tobacco smoke, soil, cosmetic products, incomplete combustion of organic materials, power plants, incinerators, refineries, forest fires, wood stoves.
Mustard gas	Pharynx, lung, and larynx cancer	Research laboratories, military personnel (war gas).
Mineral oils, untreated and mildly treated	Gastrointestinal, sinonasal, bladder, skin, bladder, lung, nasal sinuses, rectum, buccal cavity, and pharynx cancer	Lubricant, printing industry, cosmetics, medicinal and pharmaceutical preparations.

2-Naphthylamine	Urinary bladder cancer.	Dyestuffs, pigment manufacture, cigarette, industry workers.
Nickel compounds, nickel oxides and sulphides	Nasal cavity, sinuses, lung, skin cancer.	Nickel refining and smelting, metals welding, alloy mining and processing, fuels, chemical plan.
Shale oils	Skin cancer	Fuels, chemical plant feed stocks, lubricant in cotton textile industry, fuel, mining and processing.
Silica	Lung cancer	Granite, stone and glass industries.
Vinyl chloride	Liver cancer (angiosarcoma and hepatocellular)	Manufacture of vinyl chloride, chemical wastes, groundwater affected by trichloroethylene contamination.
Mists containing sulphuric acid	Laryngeal and lung cancer	Volcanic eruptions, biogenic gas emissions, oceans, packing operations, steel industry, petrochemical industry, printing, paper manufacturing, and tanneries phosphate acid.
2,3,7,8-Tetrachlorodibenzo-para-dioxine (TCDD)	Lung cancer, non-Hodgkin's lymphoma, and sarcoma	Production of pesticides, pulp and paper bleaching, polychlorinated biphenyl (PCB) production.
Acrylamide	Oral cavity, pharynx, esophagus, larynx, large bowel, kidney, breast, ovary, and Pancreas cancer	Chemical industry, waste-water treatment, sewage, textile, steel, lumber industries, petroleum refining, mineral processing, sugar production, hospitals, plastic, food packaging.
Benzidine-based dyes	Bladder and pancreatic cancer	Dyes Production, textile, paper, leather, rubber, plastics, printing, paint, and lacquer industries.
Buta-1,3-diene	Leukaemia, lymphosarcoma, reticulosarcoma, lymphopoietic cancer	Industrial & forest fires, chemical labs, plastic, rubber industries, food packaging, disposal, gasoline, automobile exhausts, cigarette smoke, petroleum refineries, automotive lead-acid batteries, incomplete fuel combustion, thermal breakdown of plastics.
α-Chlorinated toluenes (benzal chloride)	Respiratory tract cancer	Pigment, chemical industrial releases, dye, pesticide manufacture.
4-Chloro-ortho-toluidine	Urinary bladder cancer	Production industries, manufacture of dyestuffs, pigments, optical brightener, pharmaceuticals, and pesticides.
Cobalt metal with tungsten carbide	Lung cancer	Production of cemented carbides (hard-metal industry), tool grinders, saw filers, and diamond polishers.
Creosotes	Skin cancer	Brick making, wood preserving, burning of wood and coal.
Diesel engine exhaust	Lung and bladder cancer	Rail and road workers, professional drivers, dock workers, mechanics, and transport industry.
Epichlorohydrin	Lung and central nervous System cancer	Plastic production, paper manufacturing industries, synthetic leather manufacturing plants, surface water, on- and off-site landfills.
4,4-Methylene-bis(*o*-chloroaniline)	Bladder cancer	Rubber industry, production of MOCA, curing agent for roofing and wood sealing.
Lead compounds	lung, stomach, and urinary-bladder cancer	Lead smelters, plumbers, lead-acid batteries, printing press, pigment production, construction, demolition, cigarette smoke, alcoholic beverages, automobile repair worker, cable production worker, demolition worker, flame-solder worker, plumber, pottery-glaze producer, ship-repair

		worker.
Non-arsenical insecticides	Leukaemia, multiple myeloma, non- Hodgkin's lymphoma, brain and lung cancer	Production of non-arsenical insecticides, pest control, agricultural workers, flour and grain mill workers.
Polychlorinated biphenyls	Non-Hodgkin's lymphoma, Liver, and biliary tract	Production of polychlorinated biphenyls, electrical capacitor manufacturing, and research laboratories.
Tetrachloroethylene	Non-Hodgkin's lymphoma, cervix, and oesophagus cancer	Production of tetrachloroethylene, metal degreasing, and solvent.
Furan	Rat and mouse liver toxicant and carcinogen	Present in processed foods, smog, wood smoke and car exhaust.
N-nitrosamines and *N*-nitrosamides	Liver, stomach, bowel and colorectal cancer	Diet, environmentally (intestinal formation, pig caecum), tobacco smoke, workplace conditions, and cosmetics.
Acetaldehyde	Lung, throat, and oral-cavity cancer	Tobacco smokers, industries, combustion engines, power plants, burn fossil fuels, refineries, cement kilns, lumber, wood mills, paper mills, automobile and diesel exhaust.
Aluminum production	Bladder cancer	Aluminium production industries
4-Aminobiphenyl	Urinary-bladder cancer	Cigarette smoke, research laboratory.
Auramine production	Bladder tumours.	Groups of workers exposed during auramine production.
Beryllium and it's compounds	lung cancer	Beryllium miners, beryllium alloy makers, fabricators, phosphorus manufacturers, ceramics workers, nuclear reactor workers, electric and electronic equipment workers, jewellers, and cigarette.
Automotive gasoline	Stomach, kidney	Oil refineries
Carbon disulfide	Leukaemia	Rubber workers and chemical industries.
Carbon tetrachloride	Non-Hodgkin's lymphoma, and liver cancer	Chemical researchers, aircraft-maintenance workers, rubber workers, dry-cleaning machines, storage tank vents.
Dimethyl formamide	Testicular and buccal cavity cancer	Industrial workers, synthetic leather industries, tanning industries, aircraft maintenance workers, bient air near a fibre plant and waste facilities, sewage treatment plants, food packaging and pesticides.
Styrene	Leukemia, lymphoma, esophageal and pancreatic cancer	Smoking, groundwater, surface water, soil, industrial production, styrene-based polymers, motor-vehicle.
Chloroform	Colon and bladder cancer.	Chemical research laboratories.
Benzene	Leukaemia (acute myelogenous leukemia)	Shoe production industry, pharmaceutical rubber industries, printing industry, fuel, forest fires, oil seeps, industrial sources, automobile exhaust, gasoline filling stations.
Tetrachloroethylene	Non-Hodgkin's lymphoma, and oesophagus cancer	Manufacturing industries, dry cleaning, degreasing workers.
Trichloroethylene	Non-Hodgkin lymphoma, Kidney and liver cancer	Manufacturing industries, research laboratories.

Table 2 Viruses implicated in human cancer	
Virus	Human Cancer
BKV (BK Virus)	Prostate cancer
JCV (John Cunningham Virus)	Colorectal cancer, brain cancer
SV40 (Simian Virus 40)	Human malignancies, brain, bone cancer, mesothelioma
HERVs (Human Endogenous Retroviruses)	Seminomas, breast, ovarian, melanoma
HMTV (Human Mammary Tumor Virus)	Breast cancer
TTV (Torque Teno Virus)	Myeloma, gastrointestinal, lung, and breast cancer
HTLV-1(Human T-cell Leukemia Virus)	ATL (adult T-cell leukemia)
KSHV (Kaposi's Sarcoma Associated Herpesvirus) or HHV-8 (Human Herpes Hirus)	Kaposi sarcoma and primary effusion lymphoma
Hepatitis B Virus	Pancreatic cancer, and Hepatocellular carcinoma
Hepatitis C virus	HCC (liver cancer)
HPV-16,18	Cervical, oral, anogenital, penile, head and neck cancer
MCV or MCPyV (Merkel Cell Polyomavirus)	Merkel cell carcinoma (skin cancer)
EBV (Epstein-Barr Virus) or HHV-4 (Human Herpes Virus 4)	Hodgkin's lymphoma, non-Hodgkin's lymphoma, burkitt's lymphoma, nasopharyngeal carcinoma and gastrointestinal lymphoma
MMTV (Mouse Mammary Tumor Virus) or Bittner Virus	Solid tumor (carcinomas), Breast cancer
RSV (Rous Sarcoma Virus)	Malignancy, leukemia

Wood dust carcinogenesis:

Wood dust is known to be a group first human carcinogen. Listed it tenth report on carcinogenesis (2002) (38). Wood dust itself contains health hazardous substances including fungi, toxins and a number of chemical agents. It is recognised that these agents may cause irritation of oral cavity and throat, tightness of the chest, irritant dermatitis, urticaria, alveolitis, deterioration of pulmonary functions and effect on respiratory system. The chronic exposure to wood dust (some species of beech, oak, birch, mahogany, teak, and walnut) has strong association with cancer of nasal cavity, nasopharynx, and paranasal sinuses. The risk of adenocarcinoma increased with large exposure and increasing duration of wood dust exposure. In addition to those chemicals that are a part of the wood, other chemicals may be added to wood usually as preservatives, binders or glues. Common wood additive chemicals are: Substances soluble in non-polar organic solvents (Fatty acids, resin acids, waxes, alcohols (pentachlorophenol), terpenes, sterols, steryl esters, glycerols, *etc.*), Substances soluble in polar organic solvents (tannins, flavonoids, quinones, lignans, *etc.*), Substances soluble in water (carbohydrates, alkaloids, proteins (Creosote), *etc.*), Inorganic materials **(**Arsenic, Copper, Chromium, *etc.*), Urea-formaldehyde resins, Phenol-formaldehyde resins (39-40).

Carcinogenesis due to fluoridation:

In many parts of the world where drinking water contains excessive amount of fluoride (0.5-9.0 mg/L), there endemic fluorosis has been observed a serious problem. Endemic fluorosis has been reported to be an important health problem in certain parts in India, *e.g.* Andra Pradesh (Nellore, Nalgonda and Prakasam district), Haryana, Punjab, Karnataka, Tamil Nadu, and Kerala. The toxic manifestations of fluorosis are dental fluorosis (1.5mg/L intake), Skeletal fluorosis (daily intake of 3.0 to 6.0 mg/L or more), and Genu valgum. (41-42).

Fluoride is deposited in the bones during bone formation; this phenomenon may induce osteosarcoma in growing children. The evidence was of insufficient to allow confident statements about other potential harms (such as cancer and bone fracture). The amount and quality of the available data on side effects were insufficient to rule out all the biggest effects. Even though, lifetime exposure of the whole population may have large population effects. For example, an ecological study in Taiwan found a high incidence of bladder cancer in women in areas where natural fluoride content in water is high. In a recent study, Harvard University suggest that there is a connection between fluoride levels in water and osteosarcoma in young boys. However, the author recommends against drawing headlong conclusions from

this study, since a number of confounding factors had not been taken into account and that further investigation is needed (43). Recently researchers examine the possible relationship between fluoride exposure and osteosarcoma.

Radiation Carcinogenesis:

Ionising radiations can produce genetic damage, gene mutations, chromosomal aberrations, mini-satellite mutations, micronucleus formation, aneuploidy, DNA strand breaks, and chromosomal instability. Observed genetic damage can cause errors in DNA replication. Epigenetic mechanisms that alter the action of genes may also be involved in radiation induced carcinogenesis (44-45). The variety of natural and anthropogenic sources contributes over 80% exposure of ionizing radiation (not just X-rays and *γ*-radiation) to the general population. The remaining exposure to ionizing radiation is from medical procedures (15%), consumer products (3%), and other sources (<1%), which include nuclear fallout, and the nuclear fuel cycle (49).

O_2 + Ionizing radiation(hv)$\rightarrow$Free radicals $\rightarrow$ DNA damage

Ultraviolet radiation:

Over exposures of UV radiations can cause some adverse effects *e.g.* sun burn (erythema), eye damage (cataract), inflammation, immuno-suppression, premature skin aging, and increase the risk of skin cancer (melanoma and non-melanoma skin cancer). Melanoma skin cancer is less common and develops from melanocytes. Although, melanoma accounts for less than 5% of skin cancers, it is a far more serious skin cancer and it causes the majority of skin cancer deaths. (56). UV radiation can be classified in to UVA, UVB and UVC radiation. Chronic exposure of UVA and UVB radiation is responsible for visible signs of aging including rough skin, blotchy skin, wrinkled skin, sagging skin, sun burn, DNA damage (in skin cells), and skin cancer. But, UVC radiation is not normally responsible for skin cancer. The degree of cancer risk by UV radiations depends on the amount of UV exposure, the intensity of the light, length of time the skin was exposed (47).

X-rays and γ-rays radiation:

X-rays and γ-radiations are known to be a human carcinogen (Group 1). Chronic exposure to X-rays and γ-radiations is most strongly associated with salivary glands, stomach, colon, bladder, ovary, central nervous system, skin leukaemia, thyroid, breast, and lung cancer. The risk of developing these cancers, however, depends to some extent on age at exposure and amount of radiations absorbed. Childhood exposure is mainly responsible for increased the risk of leukaemia and thyroid cancer, and in adult exposure of these radiations increased the risk of breast cancer. (48).

Radon and its decay products:

Radon and its isotopic forms Radon-222 and Radon-220 are known to be human carcinogens based on sufficient evidence of carcinogenicity from studies on humans and animals. It is listed as a human carcinogen in the seventh annual report on carcinogens (1994). High exposure to radon causes lung, tracheal and bronchial cancer in humans. The risk of lung cancer increased significantly with increasing cumulative radon exposure (50).

Neutrons exposure:

Carcinogenic behaviour of neutrons have been tested in mice, rats, rabbits, dogs, and monkeys. Among these species, radiation induced tumors have been observed in different tissue sites including sites at which tumors were observed in humans (*i.e.* leukaemia, thyroid gland, breast, and lung). Susceptibility to induction of tumors depends on tissue site, species, strain, and age. The relationship between neutrons and cancer in humans are suspicious because insufficient epidemiologic evidences.

The primary exposure of neutron is natural sources but neutrons can also exposed by other anthropogenic exposures including cancer patients receiving radiation therapy, nuclear industry workers, survivors of atomic bomb blasts, airline crews and passengers. Airline crews and passengers are exposed to varying doses of neutron radiation depending on flight route, aircraft type, and number of hours in flight. Annual average equivalent doses for airline crews have been estimated to range from 0.6 to 3.6 mSv. (51).

Thorium dioxide:

Thorium dioxide is known to be a human carcinogen (Group-1). The exposure of thorium dioxide can cause a large excess of liver tumors (primarily cholangiocellular tumors and hemangiosarcoma) was observed in the thorotrast treated patients. Excess of other cancer, including bone cancer, hemangiosarcoma (in dogs and rarely in cats), and leukaemia, excluding chronic lymphoid leukaemia were increased in thorotrast treated patients. Risks were correlated with the volume of injected thorotrast. Higher exposures could occur among people living near nuclear waste sites or mining areas that contain thorium (52).

Carcinogenesis by microbiological agents:

Viruses associated with cancers:

It is estimated that viral infections contribute to major part in all human cancers. Some carcinogenic viruses are given in the (Table 2) (53-57).

Bacterial infection as a cause of cancer:

Bacterial infections have not considered major cause of cancer. More recently, however, bacteria have been connected to cancer by two specific mechanisms: induction of chronic inflammation and production of carcinogenic bacterial metabolites. The well known example of the inflammatory mechanism of carcinogenesis is *Helicobacter pylori* infection. Recently, *H. Pylori* is first bacterium declared to be Group-1 carcinogen (58). *H. pylori* infection is culpably involved in the genesis of both gastric lymphomas and gastric adenocarcinomas. The outline for the development of gastric adenocarcinomas is similar to that of HBV (Hepatitis B virus) and HCV (Hepatitis C virus) cause liver cancer. It involves raised epithelial cell proliferation in back ground of chronic inflammation. As in viral hepatitis, the inflammatory milieu has number of genotoxic agents, for example, reactive oxygen species. There is an initial development of chronic gastritis, followed by gastric atrophy, intestinal metaplasia of the lining cells, dysplasia, and cancer. This sequence takes decades to complete and occurs in only 3% of infected patients. Like HBV and HCV, the *H. Pylori* genome also has direct implication in oncogenesis. Strains linked with gastric adenocarcinoma have been shown to contain "pathogenicity island" that contains cytotoxin associated A (CagA) gene. Although *H. pylori* is non-invasive, CagA penetrates into gastric epithelial cells, where it has variety of effects including the initiation of a signalling that mimics unregulated growth factors stimulation (59-60), and other carcinogenic bacteria have been recognised that are known or suspected to cause human cancer, are *salmonella typhi* (gallbladder cancer), *Streptococcus bovis* (colorectal cancer), *Chlamydia pneumoniae* (lung cancer), *Mycoplasma* (may also have a role in the formation of different types of cancer) (61).

Natural products as carcinogens:

Tobacco and active smoking:

Tobacco smoke is a complex mixture containing over 4000 different chemicals, however, the currently identified compounds make up more than 95% of the total mass of mainstream smoke. Some of these substances cause heart, lung and other related diseases too, and all of them can be deadly. These substances are oxides of carbon and nitrogen, ammonia, hydrogen cyanide, aldehydes, ketones, alkanes, alkenes, benzene, hydrazine, vinyl chloride, polynuclear aromatic compounds, alcohols, phenols, quinones, carboxylic acids, esters, lactones, amines, amides, alkaloids, pyridines, pyrroles, pyrazines, *N*-nitrosamines, metals, agrochemicals, and chemical additives. Other substances are nickel, chromium, cadmium, tar and poison gases. Furthermore, cigarette smoke is estimated to contain over 10^{15} free radicals and very small amount of radioactive substances which can induce significant oxidative stress to play a major role in smokers getting cancer (62, 63). Cigarette smoking caused myeloid leukaemia and cancer of the nasal cavities, nasal sinus, stomach, liver, kidney (renal-cell carcinoma), uterine cervix, lung, urinary bladder, renal pelvis, oral cavity, pharynx, larynx, oesophagus, lip, and pancreatic cancer. The risk of lung cancer increases with increasing duration of smoking and with increasing numbers of cigarettes smoking per day (64).

Passive or second hand smoking:

Passive smoking is the inhalation of smoke by persons other than the intended "active" smoker. It is produced by smoking of various forms of tobacco products. Active and passive smoke contains many of the same chemical constituents including at least 250 chemicals known to be toxic and some of these chemicals are carcinogenic *e.g.* benzene, 1,3-butadiene, benzo[a]pyrene, 4-(methyl nitrosamino)-1-(3-pyridyl)-1-butanone and many others. The US, EPA (environmental protection agency) and the IARC is classified passive smoking as a "known to be a human carcinogen" in the ninth report on carcinogenesis (2000) (46). Exposure of non-smokers to environmental tobacco smoke has been determined by catching of nicotine, tobacco-specific nitrosamines, respirable smoke particulates, other smoke constituents in the breathing zone, and by measurements of a nicotine metabolite (cotinine) in the urine. Passive smoking has strong association to increase the risk of lung, breast, nasopharynx, nasal cavity, paranasal sinuses, cervix, gastrointestinal tract cancer and cancers at all sites combined (65).

Smokeless tobacco:

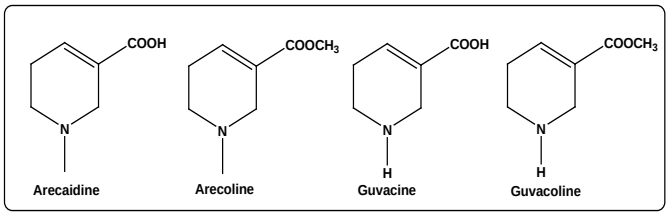
Chewing tobacco constitutes is the tobacco leaves with various sweeteners and flavorings, such as honey, licorice, rum, Snuff (dried and powered tobacco leaves), menthol, peppermint oil, camphor, aromatic additives as attar of roses, and oil of cloves. Smokeless tobacco is exposed by absorption through the oral or nasal mucosa and by ingestion. It is listed in a group of "known to be a human carcinogen". Smokeless tobacco causes cancer of the oral cavity (tumors are often arising at the site where the tobacco is placed). Extracts of smokeless tobacco

cause mutations and chromosomal aberrations in mammalian cells. Furthermore, oral-cavity tissues of smokeless tobacco users have more chromosomal damages than non-tobacco chewers (66-68).

Areca nut (betel nut):

Areca nut (fruit of the *Areca catechu* tree) is the fourth most commonly used psychoactive substance in the world after tobacco, caffeine, and alcohol. Ingredients of areca nut are carbohydrates, fats, proteins, crude fibre, polyphenols (flavonols and tannins), minerals (sodium, magnesium, chlorine, calcium, vanadium, manganese, copper, and bromine) and alkaloids (arecoline, arecaidine, guvacine and guvacoline) (69) as major constituents.

Chemical structure of areca alkaloids



The regular chewing of betel leaf with areca nut has higher risk of non-communicable diseases such as damaging their gums and acquiring cancer of the mouth, pharynx, oesophagus, liver, prostate, cervix, lung, stomach, and other disease such as obesity, asthma, acute exacerbation, diabetes mellitus, hypertension, hyperlipidemia, metabolic syndrome and cardiovascular disease. It is listed in a group of "known to be a human carcinogen". Chronic chewing of areca nut alone has been linked to cause oral sub-mucous fibrosis, pre-cancerous oral lesions and squamous cell carcinoma. Areca nut chewing also increases the risk of psychosis in patients with pre-existing psychiatric disorders [70].

Yerba mate:

Yerba mate is an experimented human carcinogen. Chronic uses of hot yerba mate are linked to the increased risk of cancer of the upper digestive tract, mainly cancer of the oesophagus. Yerba mate may also increase the risk of cancer of other tissue sites *e.g.* oropharyngeal, laryngeal, bladder, stomach, colon, rectum, lung, female breast, cervix, prostate, and kidney (only renal cell carcinoma). This carcinogenic behaviour of yerba mate is due to its polycyclic aromatic hydrocarbon (PAH) content (71). The large leaves of yerba mate expose gaseous or particle bound PAHs. Selected PAHs in yerba mate and SRM 3254 green tea leaves are naphthalene, phenanthrene, anthracene, fluoranthene, fluorine, pyrene, cyclopenta [c,d]pyrene, benzo[g,h,i] fluoranthene, benzo[c] phenanthrene, benz[a] anthracene, chrysene + triphenylene, benzo[b+j] fluoranthene, benzo[k]fluoranthene, benzo[a] fluoranthene, benzo[e]pyrene, benzo[a]pyrene, perylene, indeno[1,2,3-c,d]pyrene, benzo [g,h,i] perylene, dibenz [a,h+a,c] anthracene (72).

Safrole (shikimol):

It is a reasonably anticipated to be a human carcinogen". Safrole is regarded by the Food and Drug Administration (FDA) to be a weak carcinogen in rats. Dietary administration of safrole caused liver cancer (hepatocellular carcinoma) in male mice (73), benign or malignant liver tumors cause (hepatocellular carcinoma or adenoma or cholangiocarcinoma) in rats. Liver cancer (hepatocellular carcinoma) was also observed in mice. There is no sufficient evidences were evaluated that the relationship between human cancer and exposure specifically to Safrole (74).

Cycasin:

Cycasin is a phytotoxin compound found in Cycas revoluta and Zamia pumila plants. It is carcinogenic in mice, rats, hamsters, guinea-pigs, rabbits, fishes and it is listed to be a possibly carcinogenic to humans. Cycasin cause variety of malignant tumours mainly in the liver, kidney and intestine tumor (75).

Dietary carcinogens:

Cancer is a worldwide leading cause of death and diet is playing a substantial role in cancer etiology. The prejudicial effects of different foods, food components, and food contaminants have been widely studied in epidemiologic studies. On the basis of these studies, some food contaminants have been identified as carcinogen in humans. Diet related factors are thought to account for about 35% of cancers in developed countries. Inadequate diet and obesity increases the risk of cancer of the oesophagus, colorectum, breast, endometrium, kidney, *etc*. (76-78).

Exposure by frying (with oil):

Cooking in particular frying oils (*e.g.* rapeseed, canola, soya bean, peanut, *etc*.) at 265–275°C generates substantial amounts of airborne particulate matter (PM), the amount of these particulate matter increases with the duration of heating at high temperature. Other contaminants such as alkanes, alkenes, aldehydes, ketones, phenols, alcohols, alkanoic acids, carbonyls, polycyclic aromatic hydrocarbons (PAHs), heterocyclic amines, peroxides, hydro-peroxides, certain gaseous pollutants (*e.g.* formaldehyde, acetaldehyde, acrylamide, and acrolein) may be concentrated by prolonged heating. Some of these substances have been found to be

potential carcinogens. The chemical composition of cooking emissions varies widely depending on the cooking oils used, temperature, kind of food cooked, as well as the method and style of cooking adopted. exposures at high temperature frying are: Mixture of volatile components and PAHs **(**1,3-butadiene, benzene, benzo[a]pyrene, benz[a]anthracene, dibenz[a,h] anthr-axxxxcene, acrolein, formaldehyde, acetaldehyde), Heterocyclic amines (IQ, MeIQ, MeIQx, PhIP), Aldehydes and other volatile organic compounds: trans,trans-2,4-decadienal (t,t-2,4-DDE), it is causes lung adenocarcinoma in women's, toxicity in liver and kidney as well as induction of cell proliferation in gastrointestinal epithelial cells (79-82)

Meat cooked at high temperature:

Cooking meats at high temperature (>220^{o}C) creates heterocyclic amines that are not present in uncooked meats. Heterocyclic amines have been found in cooked beef, pork, fowl, chicken and fish product. Chronic intake of these heterocyclic amines increased the risk of developing colorectal, rectal, breast, and other cancers. Some carcinogenic heterocyclic amines and their carcinogenicity in humans are: MeIQ (rectal and colon cancer), MeIQx **[**benign colon tumors (adenoma), lung and breast cancer], IQ (breast cancer), PhIP (adenoma, breast and stomach cancer) [83, 84].

Artificial sweeteners:

The role of artificial sweeteners on cancer risk has been widely argued since 1970s, in animal study found an excess risk of bladder cancer in treatment with extremely high dose of saccharin and other artificial sweeteners or low-calorie sweeteners (mainly aspartame). High doses of these sweeteners (>1680 mg per day) cause to a high relative risk of bladder cancer in humans. Few epidemiological analyses also found association between artificial sweeteners and cancer of stomach, pancreas, endometrium, and bladder in animals and its carcinogenic effects is also species specific. There are four major commercial sweeteners, saccharin, aspartame, sucralose, and cyclamate. These have also been linked with various forms of tumor, genetic abnormalities and other chronic diseases. Neohisperidine, Acesulfame-K, sucralose and alitame are new generation sweeteners and has suspected genotoxicity or to be cause cancer (85).

Saccharin:

It has recently been identified by the Food and Drug administration as a carcinogen. The carcinogenicity of saccharin is tested by laboratory experiments and epidemiological studies provide the most reliable laboratory evidence of its carcinogenicity. According to experimental data saccharine can cause urinary bladder cancer in rats, at high doses of saccharin, especially in male rats. there is no clear evidence that saccharin causes cancer in humans, saccharin was delisted in 2000 from the U.S. National Toxicology Program's Report on Carcinogens, where it had been listed since 1981 as a substance reasonably anticipated to be a human carcinogen (86).

Cyclamate:

In 1970, however, FDA banned the use of cyclamates in all foods and drugs. This action was taken because experiments on the chronic toxicity and metabolism of a combination of (10:1 mixture of cyclamate and saccharin) cyclamate and saccharin cause bladder tumor in the rats. Other long-term studies of cyclamate on carcinogenicity and co-carcinogenicity have been conducted in laboratory animals. It is listed by the IARC in group of "Reasonably anticipated to be a human carcinogen (87).

CONCLUSION:

On the basis of this study, it is concluded that cancer may be caused mainly by chemicals, natural products, radiations, microbial agents, dietary supplements, etc.

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