SSRG International Journal of Pharmacy and Biomedical Engineering
ISSN: 2394 – 2576 / https://doi.org/10.14445/24547484/IJPBE-V9I3P101

Volume 9 Issue 3, 1-11, Sep-Dec 2022

Review Article

Current Review on Environmental Factors and Screening of Cancer

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Received: 04 October 2022 Revised: 08 Novemer 2022 Accepted: 20 November 2022 Published: 02 December 2022

Abstract *- Cancer alludes to over 277 distinct malignancies in its broadest sense. The pathogenesis of these cancers has uncovered various cancer stages in which gene mutations will play a key role. Abnormal multiplication of cells occurs due to these mutations in the genes. Environmental factors are thought to be responsible for 70-90 percent of all carcinomas. A tissue with a large number of stem cells is considered a sign of developing carcinoma in that particular tissue. The characterization of tumors is done by obtaining stem cell-like properties, which shows evidence that a stem cell-like population endures and proliferates tumors. Finding people who appear healthy in a community, have a disease in its earliest stages, or are more likely to get a condition is known as screening in the healthcare industry. An early diagnosis of an illness, which can subsequently be efficiently treated at an early stage, results in a decreased disease-specific or overall fatality. This is the aim of a screening test. In this, the effects of different environmental exposures that may impair functions of stem cells related to carcinogenesis. Several cancer screening methods were identified in the mid of the 20th century. In this article, we have discussed the effectiveness and evaluation of the screening of cancer programs in different countries. This article also established the estimated number of deaths and new cases observed worldwide in 2018. In this review, we have also established the molecular perspectives of cancer. The economic constraints related to the screening problems are also discussed.*

Keywords *- Pathogenesis, Environmental factors, Diagnosis, Screening, Molecular perspectives, Economic constraints.*

1. Introduction

Cancer is a major health problem worldwide. Consequently, carcinoma has become a significant problem that impacts the lives of all human individuals. Sadly, there is a diversity of cancer at the tissue level, so this variance is a major hurdle to diagnosis, accompanied by therapeutic efficacy. [1, 2] The following kinds of cancers are the most prevalent in men, i.e., prostate, lung and bronchus, colon and rectum, and urinary bladder. Breast cancer, lung and bronchus cancer, colon and rectum cancer, uterine corpus cancer, and thyroid cancer are most commonly observed in women. According to the statistics, prostate and breast cancer comprise a considerable portion of malignancy in both men and women. [3] Hematologic cancer and cancers of the brain & lymph nodes make up the number of cancer cases in children. [4, 5] cancer is caused by a succession of gene changes that cause the cell's functions to be altered. Chemical substances are well known for their function in the formation of gene mutations and cancer cells. Furthermore, smoking contains a number of carcinogenic chemical components that cause lung cancer. [6] Environmental chemical compounds with carcinogenic qualities, for example, affect the cytoplasm and nucleus of cells directly or indirectly, resulting in genetic abnormalities and gene alterations. [7-10]The other carcinogenic agents contributing to cancer are viruses, bacteria, and radiation, accounting for 7% of cancer cases. [11] Cancer generally alters cellular relationships and causes critical genes to malfunction. This disrupts the cell cycle, resulting in aberrant proliferation. [12, 13] Furthermore, the absence of anti-oncogenes causes uncontrollable cell division. [14] Repair genes normally code for proteins and enzymes with repairing characteristics, and there are as many as 30 types of repair proteins are identified. [15] Removing uracil from DNA prevents damage to the DNA and removes the primary Ultraviolet induced DNA lesions, which are ultimately the repair genes' jobs. [16]

2. Cancer from a Molecular Perspective

Oncogene generation and genetic disorders are caused by genetic changes such as amplification (N-myc in neuroblastoma), point mutation (Ras gene in colon cancer), deletion (Erb-B gene in breast cancer), and insertion activation (C-myc in acute blood cancer), chromosomal translocation (gene Bcr and oncogene Abl in chronic blood cancer). Chronic lymphoblastic leukaemia in adults is caused by a genetic switch between chromosomes 9 and

22. This condition induces the production of ph1, a biomarker that can aid in diagnosis and is observed in 95 % of patients. A unique gene combination is produced when the Bcr gene is coupled to the Abl oncogene, resulting in a protein with kinase activity. [17–20] An atypical cancer is caused by a mutation in the p53 gene in the development of an atypical protein that plays a vital role in disrupting p53-related biological processes. Because errors in these molecular and biological events lead to the creation of cancer cells, the p53 gene has a convoluted relation with cancer, with mutations in the p53 gene being seen in 60% of cancer cases. In general situations, p53 is involved in cellular division, apoptosis, ageing, angiogenesis, differentiation, and DNA metabolism. Furthermore, in most of the p53 genes, a sudden change occurs in the DNA-binding region, and p53 is the gene that causes gene replication failure. P53's anti-cancer properties are achieved through three mechanisms: DNA-repair protein stimulation, apoptosis activation, and cell cycle arrest in the G1 or S phase. [14, 21-27] Gene mobility, loss, and chromosomal instability are all exacerbated when hypomethylation occurs in repeated sequences. [28, 29] hypomethylation has been linked to a number of cancers, including breast, lung, and bladder cancers. [30] Hypo methylation is exemplified by L1, a member of the LINE family. In contrast to widespread hypomethylation, hypermethylation occurs in a single CpG site. Hypermethylation of promoters inhibits transcription, affecting genes involved in DNA repair (Hmlh1, WRN, and BBRCA1), vitamin response (CRBP1, RARB2), cell cycle control (P16INK4b, P16INK4a), and apoptosis (Hmlh1, WRN, and BBRCA1) (TMS1, DAPK1, and WIF-1). These occurrences are crucial in the progression of cancer. [31] Hypermethylated promoters can be considered novel biomarkers for the diagnosis and prognosis of cancer, as most research focuses on the CpG regions of promoters. Furthermore, it is essential to note that abnormal methylation, such as hypermethylation in the CpG region, is widespread (45-65%) during cancer. [32, 33] Because DNMT1 and DNMT3b have been reported to have significant levels of expression in many tumours, DNMT regulation difficulties can affect overall DNA methylation patterns. Furthermore, miRNA has been found to alter DNMT expression, and the MIR-29 family has been found to (indirectly) suppress the expression of DNMT3a, DNMT3b, and DMNT1. [34] The expression of histone methyltransferases and demethylases alters the distribution of histone methylation. It is primarily due to the production of histone methyltransferases and demethylases. Furthermore, severe mutations in SETD2 (a histone methyltransferase) and UTX (a histone demethylase) occur during renal malignancy. [35]

3. Environmental Factors

3.1. Chemical Factors

3.1.1. Heavy Metals

Arsenic

Long-term exposure to arsenic causes immortalized human cells from a number of organs to acquire cancer stem cell-like features, including the lung [36, 37], prostate [38], bladder [39], and mammary gland [40]. Consistent molecular changes were identified across all cell types, including increased matrix metalloproteinase secretion, colony development, invasion, and gene expression of stem cell markers. There has been induced overexpression of miR-143, which belongs to the family of miRNA which induces downregulation with arsenic modification, lessening the CSC phenotype and also reducing MMP-2 and MMP-9 release, cell growth, and apoptosis tolerance, which were all detected in the physiological examination of prostate epithelial cells following an 18-week exposure to inorganic arsenic at a concentration of 5 M. [41] Prostate epithelial cells which are exposed to arsenic have enhanced secretion of exosomes by 700% when assimilating with the original clone. Analysis of Exosomes obtained from arsenic-transformed cells was done, and transforming genes, inflammatory mRNA transcripts, and family of miRNAs related to oncogenesis were also identified. Separation of non - transformed prostate epithelial stem cells from the cells treated with arsenic cells stimulated a phenotype in the non-transformed cells as evidenced by an increase in the secretion of matrix metalloproteinase and epithelial-mesenchymal transition phenotype. [42]

Cadmium

Heavy metals, such as cadmium, is a probable carcinogens, with research linking it to lung cancer in the workplace. [43]The most prevalent entrance points are the industrial environment, consuming foods contaminated with cadmium, and consuming tobacco. Cadmium's effect on carcinoma, as well as stem cell routes, has now been studied in various experimental models. A low dose of (1 M) cadmium exposed to human ductal pancreatic epithelial cells in vitro resulted in enhanced spheroidal development, S100p, a pancreatic cancer marker, is overexpressed, enhanced ability to be intrusive, and recognized stem cell factors are overexpressed such as CD44 and OCT4. [44] Stem cell alterations and breast cancer occurrence on exposure to cadmium are contradictory. According to multiple case-control studies, cadmium concentration in urine is higher in breast cancer patients than in controls. [45]Follow-up research findings on the risk for breast cancer connected to approximated nutritional heavy metals like cadmium uptake have mostly been inconclusive. [46]Furthermore, there is mounting evidence that poisoning with cadmium can impair physiological mechanisms and developmental and stem ness techniques. On the other hand, exposure to cadmium has been shown to impair cellular functions and processes involved in growth and stemness. The in-utero revelation of Sprague-Dawley rats to cadmium at a concentration of 0.5 g/kg on 12 and 17 days of pregnancy stimulates estrogen in the forming mammary gland, resulting in a higher proportion of terminal end buds [47, 48], components with a high concentration of stem cells related to mammary glands. [49]

Hexavalent Chromium

It is a well-known cause of cancer linked to lung carcinoma in the workplace. [50]As per this study, the deregulation of stem cell-associated processes could be a source of Cr (VI) -related malignancy. MiR-143 is a potent inducer of IGF-IR/ IRS1 signaling, tumor development, & angiogenesis, which was shown to be 35-fold lower in the hexavalent chromium-transformed cells. [51] BEAS-2B cells were treated with 250 nm. hexavalent chromium for 20 or 40 weeks showed significant epigenetic changes, including elevations in the restrictive chromatin marks, which are H3K9me2 and H3K27me3, G9a, SUV39H1, EZH2, and GLP are histone methyltransferases. Fascinatingly, shRNA downregulation of histone methyltransferases like G9a, SUV39H1, and EZH2 substantially decreased development in non-transformed BEAS-2B following exposure to a concentration of 125 nm. Cr (VI) exposure for 25 weeks, compared with the control group of shRNA BEAS-2B cells, suggests that up-regulation of such histone methyltransferases may be necessary for promoting stem ness.[52]Upon anchorage-independent development inside the secondary spheroid study in BEAS-2B cells modified after a three-month repeated exposure to 100 nm chromate, a subgroup comprising cancerous stem cells was discovered. The tumor initiation potential of those stem cells which were exposed to chromium was greatly boosted in immune-challenged mice, as was the expression of Notch 1which is a stem cell regulator. The development of reactive oxygen species will be reduced by the decreased susceptibility to the cisplatin& escalated glycolysis was observed in the people with cancerous stem cells, which was linked to a decrease in the expression of gluconeogenesis rate-limiting enzyme, i.e., FBP1. [53] Treatment with chromium at a concentration of 0.5-2 M results in increased expression of Vimentin and SMA (mesenchymal markers) and Nanog and CD133 (stem cell markers) in a concentration-dependent manner, in HK-2, an immortalized human kidney cell line. The alterations were connected to a decrease in the expression of dihydrodiol dehydrogenase, indicating the metabolic changes may be driving chromate impacts on stem ness and stem ness-related pathways.[54] These findings imply that both epigenetic alterations are occurring, metabolic changes could be a major driver in chromium-induced cancer, and further investigation into the confluence of these biological processes is needed.

3.1.2. Tobacco Smoke

Tobacco use is linked to various malignancies, including lung carcinoma, colorectal cancer, and stomach and liver cancers, & it is calculated that tobacco use kills nearly 10 million people each year. [55, 56] The genotoxic effects of tobacco smoke's diverse blend of compounds have been widely studied. [57] Tobacco smoke and nicotine have been shown to impact stem cell-related cancer processes in multiple organs. In the following exposure of mice to tobacco smoke and the p38 inhibitor SB203580 at a concentration of 1 mg/kg B.W. for twelve weeks, the tobacco smoke-induced increase of stemness markers CD133, Nanog, & Oct4 were suppressed. [58]

3.1.3. Endocrine-Disrupting Chemicals (EDCs)

Diethylstilbesterol (DES): EDCs are becoming a growing source of worry for human health, especially in vulnerable phases of development. The women in the group who had been subjected to DES in utero have contributed significantly according to our perspective of the impact of contact with hormone-simulating chemicals throughout the development and the chance of cancer in the future. Beginning in the 1940s, it was recommended for women who were a strong probability of miscarriages. [59] By the 1970s, doctors had seen a rise in the prevalence of uncommon vaginal adenocarcinomas in females subjected to DES in utero. [60] Breast cancer risk was also found to be higher in these "DES daughters" in follow-up investigations. [61] Mechanistic investigations of ordinary mammary stem cells indicated that exposure to a concentration of 70 nmol/L DES for three weeks resulted in epithelial progeny with widespread epigenetic remodelling, including miRNA changes. The repressive H3K27me3 mark was increased when miR-9-3, an essential regulator of p53-related apoptosis, was down-regulated. [62]

3.1.4. 2, 2 -Bis (4-Hydroxyphenyl) Propane

Also known as Bisphenol-A (BPA) is a widely used plasticizer and xenoestrogen that has been discovered in 95% of the U.S. population. [63, 64] In a study of CD-1 mice exposed to Bisphenol-A in utero, the pregnancy mice progeny were given a 25 g/kg BPA concentration by intraperitoneal (I.P.) injection from E8.5-E18.5 had substantial mammary abnormalities as a contrast to the given control of sesame oil. [64]

Bisphenol Analogs

Even though Bisphenol-A is being taken out of the commercial market due to accumulating evidence that this is harmful to human health that its counterparts, BPS, BPAF, BPF, and BPB, which are structurally identical, have disruptive endocrine properties via mechanisms of estrogen-mimicking and oxidative stress. BPAF was found to be having 20 times more binding capacity for E.R. when compared to BPA in MCF-7 human breast cancer cells. [65] Treatment of the rat sperm in the laboratory with the bisphenol analogs had increased the superoxide dismutase, and reactive oxygen species (ROS) increased significantly compared to the standards at 100g/L. [66] In vitro treatment of rat sperm with BPA, BPB, BPAF, and BPAF Inflammation was also significantly higher in the bisphenol analog-exposed groups, as evaluated by phagocytes, plasma cells, and infiltration of macrophages. Neurons that produce gonadotropin-releasing hormones control the reproduction behaviour, and the neurons' size has been connected to their function. The size of GnRH neurons was significantly reduced after a low dosage, long-term exposure to Bisphenol-F at a concentration of 0.25 M in the developing embryos of zebrafish. [67] While the toxicity of BPA has been thoroughly researched and defined, the same cannot be said about its equivalents. These findings, taken together, show that BPA analogs have substantial endocrine disruptive properties, primarily

via mimicking estrogen & oxidative stress mechanisms, calling its safeness beyond doubt for broad use.

3.1.5. Parabens

Parabens, a kind of EDC often used as a preservative in cosmetics, have recently been investigated as possible cancer-causing agents for the breast. Methylparaben, an example of a compound that belongs to the class of parabens, may be found in urine samples from 99.1% of Americans; mammalian breast tissue & breast milk are also included. [68, 69] The results imply that paraben exposure affects the differentiation & multiplication of breast stem cells. On the other hand, with greater research focusing on changes, it would be desirable to have more stem cells in number. It has been shown to increase lipid accumulation in various cell lines and stem cells derived from adipose and change breast development and proliferation in cancerous breast cells. [70, 71] Adipokines that have a role in inflammation have a varied effects on mammary stem cell self-renewal. [72, 73]

3.1.6. Perfluoroalkyl Substances (PFAS)

Because of their durability, PFAS is a form of surface-active agent utilized in commerce and industry that's become an increased source of concern for the health of human beings in the environment long after they have been phased out of manufacturing. Perfluoro octane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) are the most regularly utilized, and their disruptive endocrine properties have been examined lately in vitro and in vivo. Neither estrogenic activity nor cell proliferation was stimulated when T47D hormone-dependent carcinoma cells were subjected to PFOS / PFOA at a concentration of 1012 to 104M individually.[74]

3.1.7. Pesticides

Pesticide exposure is linked to cancer at numerous tissue sites, according to growing data. [75] Organochlorines (O.C.s) are environmentally persistent pesticides that have been outlawed in several countries for more than 20 years. [76] DDT is a long-lasting pesticide that is now used to remove insects like mosquitoes in areas with a high vector-borne disease prevalence. [77, 78] Researchers used gas chromatography to remove organochlorine pesticides from breast cancer patients' tissue samples in an Egyptian comparative cross-sectional study. According to the researchers, organochlorines such as DDT are most widely utilized around the globe and can be found in the environment. Examples of pesticides like hexa-chlorobenzene, chlordane, methoxychlor, and DDT have been linked to a rise in malignancies, most likely due to tumor promotion, immunosuppression, and endocrine disruption. [76] DDT is another EDC associated with reproductive problems due to early puberty and malignancies of the germline. [79] DDT is a proven human carcinogen widely used in low- and middle-income areas. [78, 80]

3.2. Biological Factors

3.2.1. Human papillomavirus (HPV)

As per statistics from the Us National Health and Nutrition Examination Survey (Confidence interval 95%: 5.7-8.3%), the HPV is present among 6.9 percent of the population of men and women who were aged between 14 and 69. A type of OSCC: oropharyngeal squamous cell carcinomas, is caused by HPV. [81] HPV16 and HPV18 are the most carcinogenic strains, accounting for fifty to ninety percent of HNSCCs: HPV-positive head and neck squamous cell carcinomas. [81, 82] The presence of cancer stem cells in the patients with HPV16-positive oropharyngeal squamous cell carcinomas is 62.5 times more than compared patients with HPV16-negative oropharyngeal squamous cell carcinomas if aldehyde dehydrogenase was considered as a biomarker of cancerous cells stem ness in HPV16-associated oropharyngeal squamous cell carcinomas. [83] No statistically significant difference in CSC proportions when CSCs were isolated from the cultures of Human papillomavirus-positive & negative HPV-positive head and neck squamous cell carcinomas. [84] There are mutations related to CSCs and HPV in HPV-associated cervical malignancies. [82, 85]

3.2.2. Hepatitis

Hepatocellular carcinomas (HCC) are malignancies caused predominantly by infections due to Hepatitis B or Hepatitis C, but they can also be caused by liver damage or alcohol addiction. [55, 86] Hepatitis B& Cstrains account for 32 percent of infection-related malignancies in developing nations, while HBV and HCV account for 19 percent of all the infection-related cancers in industrialized countries. Hypomethylation was evaluated among HCC patients at the Prince of Wales Hospital in Hong Kong in a study aimed at determining HCV and HBV pathways to produce abnormal transcriptional enhancers. Specific enhancer C/EBP hypomethylation was linked to a lower survival rate in HCC patients when their methylomes were examined (H.R.: 4.4, p b .005). The global enhancer activity was lowered when C/EBP was removed, resulting in less invasion and colony formation. [86] In hepatitis-related malignancies, clinic pathological examination of human liver tumours has repeatedly revealed increased stemlike oval cells. [87] As oval cells are bipotent cells that can differentiate into both bile duct epithelial cells and hepatocytes, activating them is a crucial first step in liver regeneration. [88] Increased inflammatory signalling inside the stem cell niche, driven by invading immune cells, is one of the key mechanisms suggested for this growth. [89]

3.3. Physical Factors

The cohort of survivors of the atomic bomb blasts in Hiroshima and Nagasaki provides some of the finest data that supports the windows of susceptibility concept in human populations. Survivors are more likely to develop cancer in a variety of tumour types, such as thyroid [90], breast [91], and skin [92]. Early-life atomic bomb radiation exposure was significantly more related to later-life cancer incidence than later-life exposure for each of these tumour

types, indicating that the effects of early-life radiation exposure endure throughout life. [93] Radiation has been related to cancer in a variety of ways. Sunlight is essential for human health, particularly as it is required for synthesizing Vitamin D in the body. [94] UVA light has a wavelength of 315-400 nm, UVB light has a wavelength of 280-315 nm, and UVC light has a wavelength of 100-280 nm. [94, 95] DNA damage, inflammation, skin aging, and melanoma have all been linked to UVB and UVC rays. [94, 95] U.V. light is also commonly employed in biotechnology, research, and medicine for cleanliness. [95] The potential cancer-causing environmental exposures are illustrated in (Fig. 1). [96]

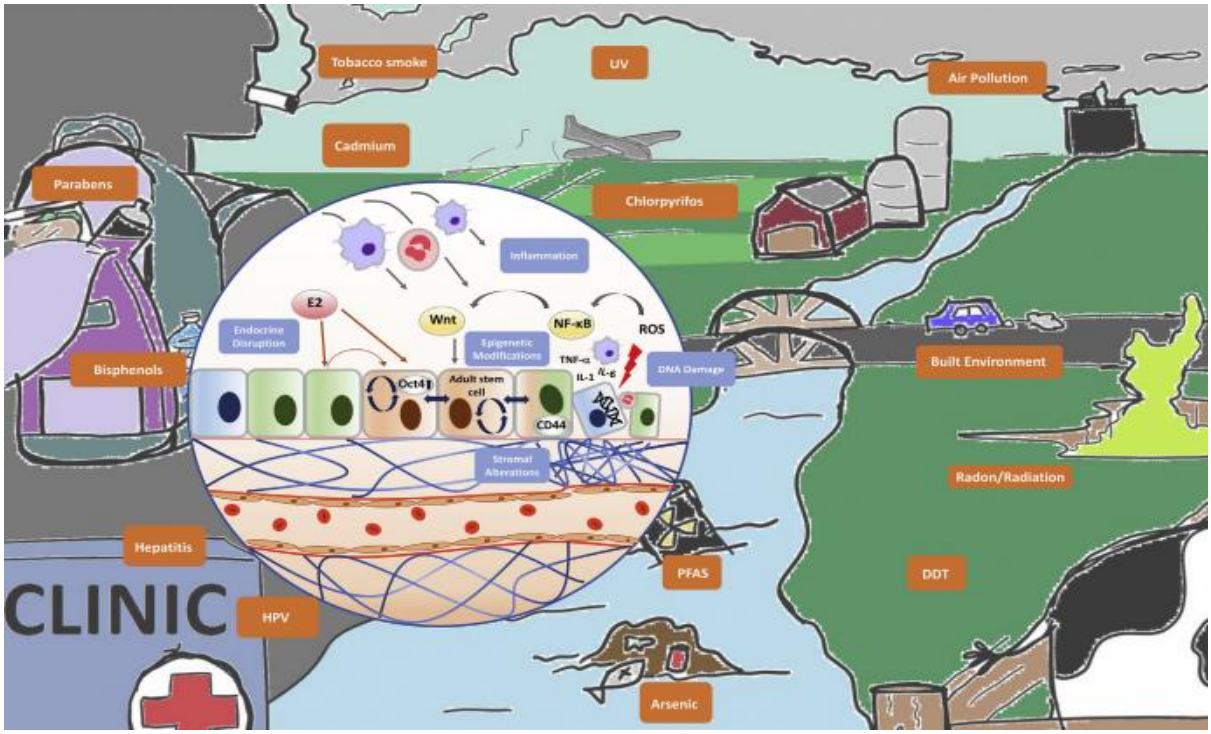

Fig. 1 Potential environmental exposures that could affect the stem cell microenvironment. [96]

4. Cancer Screening and its Role in the Control

Cancer screening is a type of secondary prevention that involves administering a battery of tests to people who appear to be healthy to identify those who are likely to have risk factors or are in the initial stages of a disease. [97] Secondary cancer prevention is just as important as primary cancer prevention in a person's preventive health plan, as it focuses on detecting and treating early invasive disease to reduce the morbidity and risk of mortality associated with a diagnosis of advanced disease, as well as detecting precursor lesions that could be potentially precancerous and predictive of final malignancy and treating them to prevent progression to invasive disease. The two main instances are detecting precancerous lesions of the cervix and colorectal adenomas. Because invites are sent out regularly when screening is due then, higher rates of participation are feasible. It results in direct outreach to the entire eligible population. If a patient needs additional imaging or biopsy, this can be tracked using the same centralized system and may be traced until the follow-up examination or test is completed. Monitoring quality assurance issues and ongoing reviews of the program's effectiveness are common features of a well-organized program. In the primary care context, applying the features of an organized system and, to the extent practicable, practicing population-based medicine improves cancer screening success measurably. Risk assessment and using office tools for reminders and tracking cancer screening are two critical components of successful cancer screening in the primary care context. (Fig. 2 & Fig. 3) illustrates the projected number of new cancer cases and fatalities worldwide in 2018. [98]

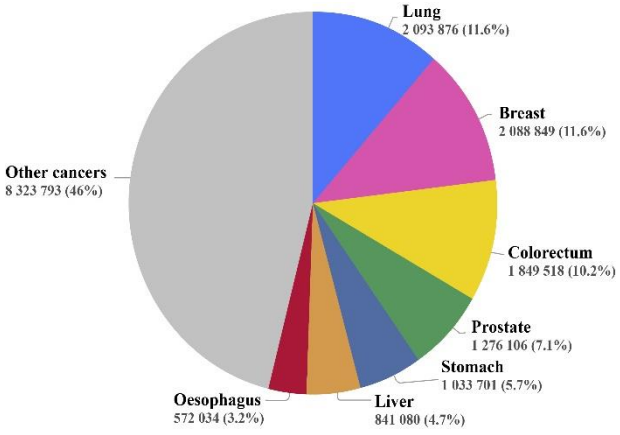

Fig. 2 Estimated number of new cases in 2018 worldwide, both sexes, all ages (Data source: Globocan 2018. Graph production: Global Cancer Observatory (http://gco.iarc.fr).) [98]

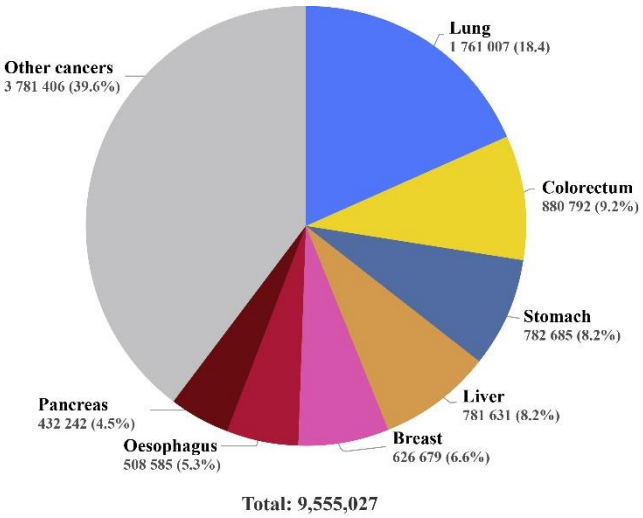

Fig. 3 Estimated number of deaths in 2018, worldwide, both sexes, all ages (Data source: Globocan 2018 Graph production: Global Cancer Observatory (http://gco.iarc.fr). [98]

5. Effectiveness and Evaluation of Cancer Screening

The ability of a screening programme to minimize morbidity and death from the disease being screened is used to determine its effectiveness. A screening test will almost certainly increase the number of diagnoses, but this should not be considered a measure of effectiveness. The screening test is considered beneficial if early detection reduces treatment-related morbidity or cancer-specific mortality. The difference in disease-specific mortality among those diagnosed by screening versus those diagnosed when presenting with symptoms is the most definite indicator of a screening program's success. Conducting well-designed randomized controlled trials (RCTs), meta-analyses, and strong case-control or case-cohort studies with low confounding factors are the best ways to measure the efficacy of screening programs. Because the study groups may not be comparable and can be affected by numerous biases, they are not considered as good as RCTs or meta-analyses. However, biases in the context of screening are not restricted to any type of study, and they apply to most of them, as they are inherent to the principles of any screening program. The four most prevalent confounding biases are as follows:

- Self-selection bias
- Lead-time bias
- Length time bias
- Over-diagnosis bias. [99]

6. Economic Considerations of Cancer Screening

Cost per quality-adjusted life-year is used to calculate the cost-effectiveness of screening (QALY). The QALY considers both the effects of longevity and the effects of quality of life. As a result, any physical or psychological side effects associated with screening-related interventions may diminish the QALY. Similarly, if screening can reduce cancer incidence while lowering the cost of treatment, screening can lower the cost per QALY. Colorectal cancer screening, for example, is cost-effective. If, on the other hand, the cancer is uncommon and no reduction in incidence can be obtained with screening, the cost per QALY can be rather expensive. The benefits of screening apply solely to individuals who are at risk, whereas the risks (overdiagnosis and screening-related side effects) apply to everyone who is screened. [99]

7. Conclusion

All the possible causes may be physical, chemical, and biological hazards and their pathways, as well as cancer-related processes. The molecular aspects of cancer-related cells have been studied. Even though there is growing evidence connecting such factors to the incidence of cancer and deregulated stemness, such hazards merely scratch the surface of the pertinent surrounding factors. Although the EPA officially classified more than 80,000 chemicals to be used in trade, we have only made a relatively finite range of assessments of these substances' carcinogenicity. We would have many opportunities to minimize disease inequalities and strengthen public safety by defining the environmental influence on stem ness throughout the life course & introducing novel agents for targeting stem cells. One of the most interesting findings concerned the function of altered genes in cancer cells. Environmental factors linked to genetic mutations have actually been found.

We can identify novel cancer biomarkers, as well as the amplitude of expression of genes and faulty proteins, using various molecular methods. Screening is a key tool based on early diagnosis and treatment concepts. A significant health cost to society, cancer frequently has unfavourable effects. Better screening and treatment advancements work in tandem with cancer screening to increase life expectancies for some malignancies. Any such programme, however, has drawbacks & dangers that could exist. Therefore, any further programme must be continuously evaluated and changed with solid justification. Through timely identification & proper care, there is the best chance to prevent cancer-related deaths in the coming days. The percentage of participants, the program's sensitivity, the handling of favourable results & prompt access to medical care all affect how efficient cancer screening is. The interconnectedness of these priorities makes it obvious that an organized care delivery system, in which each of the crucial stages that must take place is controlled by rules, roles, connections, and oversight, is beneficial for habitually attaining them.

References

[1] Meacham C and Morrison S, "Tumour heterogeneity and cancer cell plasticity". *Nature*, vol. 501, pp. 328-37. 2013. Crossref, https://doi.org/10.1038/nature12624

[2] Fisher R, Pusztai L and Swanton C, "Cancer heterogeneity: implications for targeted therapeutics". *British journal of cancer*, vol. 108 pp. 479-85, 2013. Crossref, https://doi.org/10.1038/bjc.2012.581

[3] Siegel RL, Miller KD and Jemal A, "Cancer statistics, 2016," *CA: a cancer journal for clinicians*, vol. 66, no. 1, pp. 7-30, 2016, Crossref, https://doi.org/https://doi.org/10.3322/caac.21332

[4] Schottenfeld, David and Joseph F, "*Cancer Epidemiology and Prevention*," 3rd edn, Oxford Academic, 2006.

[5] Yoo KY and Shin HR, "Cancer epidemiology and prevention," *Korean Journal of Epidemiology*, vol. 25, pp. 1-15, 2003.

[6] Aizawa K, Liu C, Tang S, Veeramachaneni S, Hu KQ, Smith DE and Wang XD, "Tobacco Carcinogen Induces Both Lung Cancer and Non-Alcoholic Steatohepatitis and Hepatocellular Carcinomas in Ferrets Which can be Attenuated By Lycopene Supplementation," *International Journal of Cancer*, vol. 139, no. 5, pp. 1171-81, 2016. Crossref, https://doi.org/https://doi.org/10.1002/ijc.30161

[7] Poon SL, McPherson JR, Tan P, Teh BT and Rozen SG, "Mutation Signatures of Carcinogen Exposure: Genome-Wide Detection and New Opportunities for Cancer Prevention," *Genome Medicine*, vol. 6, no. 24, 2014. Crossref, https://doi.org/10.1186/gm541

[8] Trafialek J and Kolanowski W, "Dietary Exposure To Meat-Related Carcinogenic Substances: Is There A Way To Estimate The Risk?" *International Journal of Food Sciences and Nutrition*, vol. 65, no. 6, pp. 774-80, 2014. Crossref, https://doi.org/10.3109/09637486.2014.917146

[9] Cumberbatch MG, Cox A, Teare D and Catto JW, "Contemporary Occupational Carcinogen Exposure and Bladder Cancer: a Systematic Review and Meta-Analysis," *JAMA Oncology*, vol. 1, no. 1, pp. 1282-90, 2015. Crossref, https://doi.org/10.1001/jamaoncol.2015.3209

[10] Antwi SO, Eckert EC, Sabaque CV, Leof ER, Hawthorne KM, Bamlet WR, Chaffee KG, Oberg AL and Petersen GM, "Exposure To Environmental Chemicals and Heavy Metals, and Risk of Pancreatic Cancer," *Cancer Causes & Control*, vol. 26, no. 11, pp. 1583-91, 2015. Crossref, https://doi.org/10.1007/s10552-015-0652-y

[11] Parkin DM, "The Global Health Burden of Infection-Associated Cancers in the Year 2002". *International Journal of Cancer*, vol. 118, no. 12, pp. 3030-44, 2006. Crossref, https://doi.org/10.1002/ijc.21731

[12] Seto M, Honma K and Nakagawa M, "Diversity of Genome Profiles in Malignant Lymphoma," *Cancer Science*, vol. 101, no. 3, pp. 573-8, 2010. Crossref, https://doi.org/10.1111/j.1349-7006.2009.01452.x

[13] Cigudosa JC, Parsa NZ, Louie DC, Filippa DA, Jhanwar SC, Johansson B, Mitelman F and Chaganti RS, "Cytogenetic Analysis of 363 Consecutively Ascertained Diffuse Large B-cell Lymphomas". *Genes, Chromosomes and Cancer*, vol. 25, no. 2, pp. 123-33,1999.

[14] Matlashewski G, Lamb P, Pim D, Peacock J, Crawford L, Benchimol S. "Isolation And Characterization Of A Human P53 Cdna Clone: Expression Of The Human P53 Gene". *The EMBO Journal*, vol. 3, no. 13, pp. 3257–3262,, 1984. Crossref, https://doi.org/10.1002/j.1460-2075.1984.tb02287.x

[15] Wei Q, Li L and Chen D, DNA Repair, Genetic Instability, and Cancer," *World Scientific*, pp. 376, 2007. Crossref, https://doi.org/10.1142/6228

[16] Wood RD, Mitchell M, Sgouros J and Lindahl T. "Human DNA Repair Genes," *Science*, vol. 291, pp. 1284-9, 2001. Crossref, https://doi.org/10.1126/science.1056154

[17] Joensuu H and Dimitrijevic S, "Tyrosine Kinase Inhibitor Imatinib (STIS71) as an Anti-Cancer Agent for Solid Tumours," *Annals of Medicine*, vol, 33, pp. 451-455, 2001. Crossref, https://doi.org/10.3109/07853890109002093

[18] King CR, Kraus MH and Aaronson SA, "Amplification of a Novel V-Erbb-Related Gene in a Human Mammary Carcinoma," *Science*, vol. 229, pp. 974-7, 1985. Crossref, https://doi.org/10.1126/science.2992089

[19] Heinrich MC, Blanke CD, Druker BJ and Corless CL. "Inhibition of KIT Tyrosine Kinase Activity: a Novel Molecular Approach to the Treatment of Kit-Positive Malignancies," *Journal of Clinical Oncology*, vol. 20, pp. 1692-703, 2002. Crossref, https://doi.org/10.1200/JCO.2002.20.6.1692

[20] Thomas RK, Baker AC, DeBiasi RM, et al, "High-Throughput Oncogene Mutation Profiling in Human Cancer," *Nature Genetics*, vol. 39, no. 3, pp. 347-51, 2007. Crossref, https://doi.org/10.1038/ng1975

[21] May P and May E, "Twenty Years of P53 Research: Structural and Functional Aspects of the P53 Protein," *Oncogene*, vol. 18, no. 53, pp. 7621, 1999. Crossref, https://doi.org/10.1038/sj.onc.1203285

[22] McBride O, Merry D, Givol D. "The Gene For Human P53 Cellular Tumor Antigen Is Located On Chromosome 17 Short Arm (17p13)," *Proceedings of the National Academy of Sciences*, vol. 83, no. 1, pp. 130-4, 1986. Crossref, https://doi.org/10.1073/pnas.83.1.130

[23] Isobe M, Emanuel B, Givol D, Oren M and Croce CM, "Localization of Gene for Human P53 Tumour Antigen to Band 17p13," *Nature*, vol. 320, pp. 84-85, 1986. Crossref, https://doi.org/10.1038/320084a0

[24] Miller C and Koeffler H, "P53 Mutations in Human Cancer," *Leukemia*, vol. 7, no. 2, pp. S18-21, 1993.

[25] Koshland Jr DE, "Molecule of the Year," *Science*, vol. 258, 1992. Crossref, https://doi.org/10.1126/science.1470903

[26] Muller PA and Vousden KH, "Mutant P53 in Cancer: New Functions and Therapeutic Opportunities," *Cancer Cell*, vol. 25, no. 3, pp. 304-17, 2014. Crossref, https://doi.org/10.1016/j.ccr.2014.01.021

[27] Selivanova G, "P53: Fighting Cancer," *Current Cancer Drug Targets*, vol. 4, no. 5, pp. 385-402, 2004. Crossref, https://doi.org/10.2174/1568009043332934

[28] Goelz SE, Vogelstein B, Hamilton SR and Feinberg AP, "Hypo Methylation of DNA from Benign and Malignant Human Colon Neoplasms," *Science*, vol. 228, no. 4696, pp. 187-91, 1985. Crossref, https://doi.org/10.1126/science.2579435

[29] Kanai Y, Hirohashi S, "Alterations of DNA Methylation Associated with Abnormalities of DNA Methyltransferases in Human Cancers During Transition from a Precancerous to a Malignant State," *Carcinogenesis*, vol. 28, no. 12, pp. 2434-42, 2007. Crossref, https://doi.org/10.1093/carcin/bgm206

[30] Wilson AS, Power BE and Molloy PL, "DNA Hypomethylation and Human Diseases," *Biochimicaet Biophysica Acta*, vol. 1775, no. 1, pp. 138-62, 2007. Crossref, https://doi.org/10.1016/j.bbcan.2006.08.007

[31] Esteller M, "Epigenetic Gene Silencing in Cancer: the Dna Hypermethylome," *Human Molecular Genetics*, vol. 16, no. 1, pp. R50-R9, 2007. Crossref, https://doi.org/10.1093/hmg/ddm018

[32] Li M, Chen W-d, Papadopoulos N, et al, "Sensitive Digital Quantification of DNA Methylation in Clinical Samples," *Nature Biotechnology*, vol. 27, no. 9, pp. 858-63, 2009. Crossref, https://doi.org/10.1038/nbt.1559

[33] Doi A, Park I-H, Wen B, et al. "Differential methylation of tissue-and cancer-specific CpG island shores distinguishes human induced pluripotent stem cells, embryonic stem cells and fibroblasts". *Nature genetics*. 2009; 41: 1350-3.

[34] Miremadi A, Oestergaard MZ, Pharoah PD, Caldas C. "Cancer genetics of epigenetic genes". *Human molecular genetics*. 2007; 16: R28-R49.

[35] Dalgliesh GL, Furge K, Greenman C, et al, "Systematic Sequencing of Renal Carcinoma Reveals Inactivation of Histone Modifying Genes," *Nature*, vol. 463, pp. 360-3, 2010. Crossref, https://doi.org/10.1038/nature08672

[36] Chang. Q, Chen. B, Thakur. C, Lu. Y and Chen. F, "Arsenic-Induced Sub-Lethal Stress Reprograms Human Bronchial Epithelial Cells to Cd61 Cancer Stem Cells," *Oncotarget*, vol. 5, no. 5, pp. 1290–1303, 2014. Crossref, https://doi.org/10.18632/oncotarget.1789

[37] Person. R. J, Ngalame. N. N. O, Makia. N. L, Bell. M. W, Waalkes. M. P and Tokar. E. J, "Chronic Inorganic Arsenic Exposure in Vitro Induces a Cancer Cell Phenotype in Human Peripheral Lung Epithelial Cells," *Toxicology and Applied Pharmacology*, vol. 286, no. 1, pp. 36-43, 2015. Crossref, https://doi.org/10.1016/j.taap.2015.03.014

[38] Tokar. E. J, Qu. W, Liu, J, Liu. W, Webber. M. M, Phang. J. M and Waalkes. M. P, "Arsenic-Specific Stem Cell Selection During Malignant Transformation," *Journal of the National Cancer Institute*, vol. 102, no. 9, pp. 638-649, 2010. Crossref, https://doi.org/10.1093/jnci/djq093

[39] Ooki A, Begum A, Marchionni L, VandenBussche C. J, Mao S, Kates M and Hoque M. O, "Arsenic Promotes the COX2/PGE2-SOX2 Axis to Increase the Malignant Stemness Properties of Urothelial Cells," *International Journal of Cancer*, vol. 143, no. 1, pp. 113–126, 2018. Crossref, https://doi.org/10.1002/ijc.31290

[40] Xu Y, Tokar E. J and Waalkes M. P, "Arsenic-Induced Cancer Cell Phenotype in Human Breast Epithelia is Estrogen Receptor-Independent but Involves Aromatase Activation," *Archives of Toxicology*, vol. 88, no. 2, pp. 263–274, 2014. Crossref, https://doi.org/10.1007/s00204-013-1131-4

[41] Ngalame N. N. O, Makia N. L, Waalkes M. P and Tokar E. J, "Mitigation of Arsenic-Induced Acquired Cancer Phenotype in Prostate Cancer Stem Cells By miR-143 Restoration," *Toxicology and Applied Pharmacology*, vol. 312, pp. 11-18, 2016. Crossref, https://doi.org/10.1016/j.taap.2015.12.013

[42] Ngalame N. N. O, Luz A. L, Makia N and Tokar E. J, "Arsenic Alters Exosome Quantity and Cargo to Mediate Stem Cell Recruitment Into a Cancer Stem Cell-Like Phenotype," *Toxicological Sciences*, vol. 165, no. 1, pp. 40–49, 2018. Crossref, https://doi.org/10.1093/toxsci/kfy176

[43] Waalkes and M. P, "Cadmium Carcinogenesis," *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, vol. 533, no. 1-2, pp. 107-20, 2003. Crossref, https://doi.org/10.1016/j.mrfmmm.2003.07.011

[44] Qu W, Tokar E. J, Kim A. J, Bell M. W and Waalkes M. P, "Chronic Cadmium Exposure in Vitro Causes Acquisition of Multiple Tumor Cell Characteristics in Human Pancreatic Epithelial Cells," *Environmental Health Perspectives*, vol. 120, no. 9, pp. 1265–1271, 2012. Crossref, https://doi.org/10.1289/ehp.1205082

[45] Gallagher C. M, Chen J. J and Kovach J. S, "Environmental Cadmium and Breast Cancer Risk," *Aging*, vol. 2, no. 11, pp. 804–814, 2010. Crossref, https://doi.org/10.18632/aging.100226

[46] Van Maele-Fabry G, Lombaert N and Lison D, "Dietary Exposure to Cadmium and Risk of Breast Cancer in Postmenopausal Women: a Systematic Review and Meta-Analysis," *Environment International*, vol. 86, pp. 1-13, 2016. Crossref, https://doi.org/10.1016/j.envint.2015.10.003

[47] Johnson M. D, Kenney N, Stoica A, Hilakivi-Clarke L, Singh B, Chepko G and Martin M. B, "Cadmium Mimics the in Vivo Effects of Estrogen in the Uterus and Mammary Gland," *Nature Medicine*, vol. 9, no. 8, pp. 1081–1084, 2003. Crossref, https://doi.org/10.1038/nm902

[48] Parodi D. A, Evans C, Williams J, Greenfield M, Cyrus K. C, Martin M. B and Martin M. B, "Alteration of Mammary Gland Development and Gene Expression by in Utero Exposure to Cadmium," *International Journal of Molecular Sciences*, vol. 18, no. 9, pp. 1939, 2017. Crossref, https://doi.org/10.3390/ijms18091939

[49] Kenney N. J, Smith, G. H, Lawrence E, Barrett J. C and Salomon D. S, "Identification of Stem Cell Units in the Terminal end Bud and Duct of the Mouse Mammary Gland," *Journal of Biomedicine and Biotechnology*, vol. 1, no. 3, pp. 133-143, 2001.

[50] Gibb H J, Lees P S J, Pinsky P. F and Rooney B. C, "Lung Cancer Among Workers in Chromium Chemical Production," *American Journal of Industrial Medicine*,vol. 38, no. 2, pp. 115-26, 2000. Crossref, https://doi.org/10.1002/1097-0274(200008)38:2<115::aid-ajim1>3.0.co;2-y

[51] He J, Qian X, Carpenter R, Xu Q, Wang L, Qi Y and Jiang B. H, "Repression of MIR-143 Mediates Cr (VI)-Induced Tumor Angiogenesis via IGF-IR/IRS1/ERK/IL-8 Pathway," *Toxicological Sciences*, vol. 134, no. 1, pp. 26-38, 2013. Crossref, https://doi.org/10.1093/toxsci/kft101

[52] Wang Z, Wu J, Humphries B, Kondo K, Jiang Y, Shi X and Yang C, "Upregulation of Histone-Lysine Methyltransferases Plays a Causal Role in Hexavalent Chromium Induced Cancer Stem Cell-Like Property and Cell Transformation," *Toxicology and Applied* Pharmacology, vol. 342, pp. 22-30, 2018. Crossref, https://doi.org/10.1016/j.taap.2018.01.022

[53] Dai J, Ji Y, Wang W, Kim D, Fai L. Y, Wang L and Zhang Z, "Loss of Fructose-1,6- Bisphosphatase Induces Glycolysis and Promotes Apoptosis Resistance of Cancer Stemlike Cells: an Important Role in Hexavalent Chromium-Induced Carcinogenesis," *Toxicology and Applied Pharmacology*, vol. 331, pp. 164–173, 2017. Crossref, https://doi.org/10.1016/j.taap.2017.06.014

[54] Li W J, Yang C. L, Chow K. C and Kuo T. W, "Hexavalent Chromium Induces Expression of Mesenchymal and Stem Cell Markers in Renal Epithelial Cells," *Molecular Carcinogenesis*, vol. 55, no. 2, pp. 182-92, 2016. Crossref, https://doi.org/10.1002/mc.22268

[55] Proctor R. N, "Tobacco and the Global Lung Cancer Epidemic," *Nature Reviews Cancer*, vol. 1, no. 1, pp. 82-6, 2001. Crossref, https://doi.org/10.1038/35094091

[56] Torre L, Bray F, Siegel R. L, Ferlay J, Lortet-Tieulent J and Jernal A "Global Cancer Statistics," *CA Cancer Journal for Clinicians*, vol. 65, no. 2, pp. 87-108, 2015. Crossref, https://doi.org/10.3322/caac.20107

[57] DeMarini D. M, "Genotoxicity of Tobacco Smoke and Tobacco Smoke Condensate: a Review," *Mutation Research, Reviews in Mutation Research*, vol. 567, no. 2–3, pp. 447–474, 2004. Crossref, https://doi.org/10.1016/j.mrrev.2004.02.001

[58] Xie C, Zhu J, Wang X, Chen J, Geng S, Wu J and Li X, "Tobacco Smoke-Induced Hepatic Cancer Stem Cell-Like Properties Through IL-33/p38 Pathway," *Journal of Experimental & Clinical Cancer Research*. 2019; 38(1):39. Crossref, https://doi.org/10.1186/s13046-019-1052-z

[59] Hilakivi-Clarke L, "Maternal Exposure to Diethylstilbestrol During Pregnancy and Increased Breast Cancer Risk in Daughters," *Breast Cancer Research*, vol. 16, no. 2, pp. 208, 2014. Crossref, https://doi.org/10.1186/bcr3649

[60] Herbst A. L, Ulfelder H, and Poskanzer D. C, "Adenocarcinoma of the Vagina. Association of Maternal Stilbestrol Therapy with Tumor Appearance In Young Women," *The New England Journal of Medicine*, vol. 284, no. 15, pp. 878-881, 1971. Crossref, https://doi.org/10.1056/NEJM197104222841604

[61] Troisi R, Hatch E. E, Titus-Ernstoff L, Hyer M, Palmer J. R, Robboy S. J and Hoover R. N, "Cancer Risk in Women Prenatally Exposed to Diethylstilbestrol," *International Journal of Cancer*, vol. 121, no. 2, pp. 356-60, 2007. Crossref, https://doi.org/10.1002/ijc.22631

[62] Hsu P. Y, Deatherage D. E, Rodriguez B. A. T, Liyanarachchi S, Weng Y. I, Zuo T and Huang T. H. M, "Xenoestrogen-Induced Epigenetic Repression of Microrna-9-3 in Breast Epithelial Cells," *Cancer Research*, vol. 69, no. 14, pp. 5936–5945, 2009. Crossref, https://doi.org/10.1158/0008-5472.CAN-08-4914

[63] Calafat A. M, Ye X, Wong L Y, Reidy J. A and Needham L. L, "Exposure of the U.S. Population to Bisphenol a and 4- Tertiary - Octylphenol: 2003–2004," *Environmental Health Perspectives*. 2008; 116(1): 39–44.

[64] Hindman A. R, Mo, X. M, Helber H. L, Kovalchin C. E, Ravichandran N, Murphy A. R and Burd C. J, "Varying Susceptibility of the Female Mammary Gland to in Utero Windows of BPA Exposure," *Endocrinology*, vol. 158, no. 10, pp. 3435–3447, 2017. Crossref, https://doi.org/10.1210/en.2017-00116

[65] Kitamura S, Suzuki T, Sanoh S, Kohta, R, Jinno N, Sugihara, K and Ohta S, "Comparative Study of the Endocrine-Disrupting Activity of Bisphenol a and 19 Related Compounds," *Toxicological Sciences*, vol. 84, no. 2, pp. 249–259, 2005. Crossref, https://doi.org/10.1093/toxsci/kfi074

[66] Ullah A, Pirzada M, Jahan S,Ullah H and Khan M. J, "Bisphenol A Analogues Bisphenol B, Bisphenol F, and Bisphenol S Induce Oxidative Stress, Disrupt Daily Sperm Production, and Damage Dna in Rat Spermatozoa: a Comparative in Vitro And in Vivo Study," *Toxicology and Industrial Health*, vol. 35, no. 4, pp. 294-303, 2019. Crossref, https://doi.org/10.1177/0748233719831528

[67] Weiler K and Ramakrishnan S, "Bisphenol F Causes Disruption of Gonadotropinreleasing Hormone Neural Development in Zebrafish via an Estrogenic Mechanism," *NeuroToxicology*, vol. 71, pp. 31-38, 2019. Crossref, https://doi.org/10.1016/j.neuro.2018.12.001

[68] Barr, L, Metaxas G, Harbach C. A. J, Savoy L. A and Darbre P. D. "Measurement of Paraben Concentrations in Human Breast Tissue at Serial Locations Across the Breast From Axilla to Sternum," *Journal of Applied Toxicology*, vol. 32, no. 3, pp. 219-232, 2012. Crossref, https://doi.org/10.1002/jat.1786

[69] Antonia M Calafat, Xiaoyun Ye, Lee-Yang Wong, Amber M Bishop and Larry L Needham, "Urinary Concentrations of Four Parabens in the U.S. Population: NHANES 2005–2006," *Environmental Health Perspectives*, vol. 118, no. 5, pp. 679–685, 2010. Crossref, https://doi.org/10.1289/ehp.0901560

[70] Hu P, Chen X, Whitener R. J, Boder E. T, Jones J. O, Porollo A and Zhao L, "Effects of Parabens on Adipocyte Differentiation," *Toxicological Sciences*, vol. 131, no. 1, pp. 56–70, 2013. Crossref, https://doi.org/10.1093/toxsci/kfs262

[71] Hu P, Overby H, Heal E, Wang S, Chen J, Shen C and Zhao L, "Methylparaben and Butylparaben Alter Multipotent Mesenchymal Stem Cell Fates Towards Adipocyte Lineage". *Toxicology and Applied Pharmacology*, vol. 329, pp. 48–57, 2017. Crossref, https://doi.org/10.1016/j.taap.2017.05.019

[72] Esper R. M, Dame M, McClintock S, Holt P. R, Dannenberg A. J, Wicha M. S and Brenner D. E, "Leptin and Adiponectin Modulate the Self-Renewal of Normal Human Breast Epithelial Stem Cells," *Cancer Prevention Research (Philadelphia, Pa.)*,vol. 8, no. 12, pp. 1174–1183, 2015. Crossref, https://doi.org/10.1158/1940-6207.CAPR-14-0334

[73] Hill E. M, Esper R. M, Simon B. R, Aslam M. N, Jiang Y, Dame M. K and Brenner D. E, "Dietary Polyunsaturated Fatty Acids Modulate the Adipose Secretome to Influence Mammary Stem Cell Self-Renewal," *Journal of Nutritional Biochemistry*, vol. 71, pp. 45-53, 2019.

[74] Sonthithai P, Suriyo T, Thiantanawat A, Watcharasit P, Ruchirawat M and Satayavivad J, "Perfluorinated Chemicals, PFOS and PFOA, Enhance the Estrogenic Effects of 17β-Estradiol in T47D Human Breast Cancer Cells," *Journal of Applied Toxicology*, vol. 36, no. 6, pp. 790–801, 2016. Crossref, https://doi.org/10.1002/jat.3210

[75] Mostafalou, S and Abdollahi M, "Pesticides And Human Chronic Diseases: Evidences, Mechanisms, And Perspectives," *Toxicology and Applied Pharmacology*, vol. 268, no. 2, pp. 157-77, 2013. Crossref, https://doi.org/10.1016/j.taap.2013.01.025

[76] Eldakroory S, Morsi El D, Abdel-Rahman R, Roshdy S, Gouida M and Khashaba E, "Correlation Between Toxic Organochlorine Pesticides and Breast Cancer," *Human & Experimental Toxicology*, vol. 36, no. 12, pp. 1326–1334, 2017. Crossref, https://doi.org/10.1177/0960327116685887

[77] International Agency for Research on Cancer (2015)"DDT, lindane and 2,4-D," IARC Working Group. Lyon. (2–9 June, IARC MonogrEvalCarcinog Risks Hum).

[78] Sapbamrer R, Prapamontol T, Prakobvitayakit O, Vaneesorn Y, Mangklabruks A and Hock, B, "Placental Transfer of DDT In Mother-Infant Pairs from Northern Thailand," *Journal of Environmental Science and Health - Part B Pesticides, Food Contaminants, and Agricultural Wastes*, vol. 43, no. 6, pp. 484–489, 2008.

[79] Strong A, Shi Z, Strong M, Miller D, Rusch D, Buechlein A et al, "Effects of the Endocrine-Disrupting Chemical DDT on Self-Renewal and Differentiation of Human Mesenchymal Stem Cells," *Environmental Health Perspectives*, vol. 123, no. 1, pp. 42-48, 2015. Crossref, https://doi.org/10.1289/ehp.1408188

[80] Aamir M, Khan S and Li G, "Dietary Exposure to HCH and DDT Congeners and Their Associated Cancer Risk Based on Pakistani Food Consumption," *Environmental Science and Pollution Research*, vol. 25, no. 9, pp. 8465-8474, 2018. Crossref, https://doi.org/10.1007/s11356-017-1129-1

[81] Gillison, M. L, Broutian T, Pickard R. K. L, Tong Z. Y, Xiao W, Kahle L and Chaturvedi A. K, "Prevalence of Oral HPV Infection in the United States, 2009-2010," *JAMA: The Journal of the American Medical Association*, vol. 307, no. 7, pp. 693–703, 2012. Crossref, https://doi.org/10.1001/jama.2012.101

[82] Pullos A. N, Castilho R. M and Squarize C. H, "HPV Infection of the Head and Neck Region and its Stem Cells," *Journal of Dental Research, vol.* 94, no. 11, pp. 1532–1543, 2015. Crossref, https://doi.org/10.1177/0022034515605456

[83] Zhang M, Kumar B, Piao L, Xie X, Schmitt A, Arradaza N, Pan Q, "Elevated Intrinsic Cancer Stem Cell Population in Human Papillomavirus-Associated Head and Neck Squamous Cell Carcinoma," *Cancer*, vol. 120, no. 7, pp. 992–1001, 2014. Crossref, https://doi.org/10.1002/cncr.28538

[84] Tang A. L, Owen J. H, Hauff S. J, Park J. J, Papagerakis S, Bradford C. R and Prince M. E, "Head and Neck Cancer Stem Cells". *Otolaryngology-Head and Neck Surgery*, vol. 149, no. 2, pp. 252–260, 2013. Crossref, https://doi.org/10.1177/0194599813486599

[85] Tyagi A, Vishnoi K, Mahata S, Verma G, Srivastava Y, Masaldan, S and Das B. C, "Cervical Cancer Stem Cells Selectively Overexpress HPV Oncoprotein E6 that Controls Stem Ness and Self-Renewal Through Upregulation of HES1," *Clinical Cancer Research*, vol. 22, no. 16, pp. 4170–4184, 2016. Crossref, https://doi.org/10.1158/1078-0432.CCR-15-2574

[86] Xiong L, Wu F, Wu Q, Xu L, Cheung OK, Kang W, Mok MT, Szeto LLM, Lun CY, Lung RW, Zhang J, Yu KH, Lee SD, Huang G, Wang CM, Liu J, Yu Z, Yu DY, Chou JL, Huang WH, Feng B, Cheung YS, Lai PB, Tan P, Wong N, Chan MW, Huang TH, Yip KY, Cheng AS and To KF, "Aberrant Enhancer Hypomethylation Contributes to Hepatic Carcinogenesis Through Global Transcriptional Reprogramming," *Nature Communications*, vol. 10, no. 1, pp. 335, 2019. Crossref, https://doi.org/10.1038/s41467-018-08245-z

[87] Hsia CC, Evarts RP, Nakatsukasa H, Marsden ER and Thorgeirsson SS, "Occurrence of Oval-Type Cells in Hepatitis B Virus Associated Human Hepatocarcinogenesis," *Hepatology*, vol. 16, no. 6, pp. 1327–1333, 1992. Crossref, https://doi.org/10.1002/hep.1840160604

[88] Erker L and Grompe M, "Signaling Networks in Hepatic Oval Cell Activation," *Stem Cell* Research, vol. 1, no. 2, pp. 90–102, 2008. Crossref, https://doi.org/10.1016/j.scr.2008.01.002

[89] Libbrecht L, Desmet V, Van Damme B and Roskams T, "Deep intralobular extension of human hepatic "Progenitor Cells" Correlates with Parenchymal Inflammation in Chronic Viral Hepatitis: Can "Progenitor Cells" Migrate?," *Journal of Pathology*, vol. 192, no. 3, pp. 373-8, 2000. Crossref, https://doi.org/10.1002/1096-9896(2000)9999:9999<::AID-PATH700>3.0.CO;2-5

[90] Prentice RL, Kato H, Yoshimoto K and Mason M, "Radiation Exposure and Thyroid Cancer Incidence Among Hiroshima and Nagasaki Residents," *Natl Cancer Inst Monograph*, vol. 62, pp. 207-12, 1982.

[91] Land CE, Tokunaga M, Koyama K, Soda M, Preston DL, Nishimori I and Tokuoka S, "Incidence of Female Breast Cancer Among Atomic Bomb Survivors, Hiroshima and Nagasaki, 1950-1990," *Radiation Research*, vol. 160, no. 6, pp. 707–717, 2003. Crossref, https://doi.org/10.1667/rr3082

[92] Ron E, Preston DL, Kishikawa M, Kobuke T, Iseki M, Tokuoka S, Tokunaga M and Mabuchi K, "Skin Tumor Risk Among Atomic-Bomb Survivors In Japan," *Cancer Causes & Control*, vol. 9, no. 4, pp. 393-401, 1998. Crossref, https://doi.org/10.1023/a:1008867617415

[93] Douple E, Mabuchi K, Cullings H, Preston D, Kodama K, Shimizu Y et al, "Long-Term Radiation-Related Health Effects In A Unique Human Population: Lessons Learned From The Atomic Bomb Survivors Of Hiroshima And Nagasaki," *Disaster Medicine and Public Health Preparedness*, vol. 5, no. S1, pp. S122-S133, 2011. Crossref, https://doi.org/10.1001/dmp.2011.21

[94] Notara M, Refaian N, Braun G, Steven P, Bock F and Cursiefen C, "Short-Term Uvb-Irradiation Leads to Putative Limbal Stem Cell Damage and Niche Cell-Mediated Upregulation of Macrophage Recruiting Cytokines," *Stem Cell Research*, vol. 15, no. 3, pp. 643–654, 2015. Crossref, https://doi.org/10.1016/j.scr.2015.10.008

[95] Wong DY, Ranganath T and Kasko AM, "Low-Dose, Long-Wave UV Light Does Not Affect Gene Expression of Human Mesenchymal Stem Cells," *PLoS One*, vol. 10, no. 9, pp. 1–21, 2015. Crossref, https://doi.org/10.1371/journal.pone.0139307

[96] Thong T, Forté C, Hill E and Colacino J, "Environmental Exposures, Stem Cells, and Cancer," *Pharmacology & Therapeutics*, vol. 204. pp. 107398, 2019. Crossref, https://doi.org/10.1016/j.pharmthera.2019.107398

[97] Morrison A, *Screening in chronic disease*. New York: Oxford University Press, vol. 4, pp. 565–566, 1993. Crossref, https://doi.org/10.1007/BF00052433

[98] Smith R and Oeffinger K, "The Importance of Cancer Screening," *Medical Clinics of North America*, vol. 104, no. 6, pp. 919-938. 2020. Crossref, https://doi.org/10.1016/j.mcna.2020.08.008

[99] MihirChandarana, Kapila Shrestha and Rishikesh Parmeshwar, "Principles of Cancer Screening," *Surgery (Oxford)*, vol. 39, no. 4, pp. 221-227, 2021. Crossref, https://doi.org/10.1016/j.mpsur.2021.01.016