

***Corresponding author**

*Muhammad Waqar Mazhar,
Department of Bioinformatics and
Biotechnology, Government College
University, 38000Faisalabad, Paki-
stan.

***Key Words:**

Chemotherapy, clinical profile, he-
matological changes, cardiovascular
effects, cancer patients

**Pre- and Post-Analysis of the Clinical Profile of
Cancer Patients before and after Chemotherapy**

Muhammad Waqar Mazhar*

*Department of Bioinformatics and Biotechnology, Government College Univer-
sity, 38000Faisalabad, Pakistan.*

Abstract

Chemotherapy, a cornerstone in cancer treatment, significantly alters the clinical profiles of patients, necessitating thorough pre- and post-treatment analyses. This review synthesizes findings from multiple studies to elucidate the impact of chemotherapy on various physiological and biochemical parameters. Key observations include significant decreases in systolic and diastolic blood pressure, white blood cell (WBC) count, and red blood cell (RBC) count post-chemotherapy. Hemoglobin and hematocrit levels also show notable declines, underscoring the onset of severe anemia. Interestingly, high-density lipoprotein (HDL) levels increase significantly, though the mechanisms remain unclear. Parameters such as platelet count, uric acid, and creatinine, cholesterol, low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), and triglycerides exhibit changes that are not statistically significant. The findings highlight the critical need for vigilant monitoring and proactive management of hematological and cardiovascular parameters to mitigate the adverse effects of chemotherapy. This review underscores the importance of a holistic approach to patient care to optimize therapeutic outcomes and improve the quality of life for cancer patients undergoing chemotherapy.

Introduction

Globally, cancer is a major threat to public health. It is among the most dangerous and catastrophic diseases of the twenty-first century and ranks as the second most common cause of mortality (Marcellin & Kutala, 2018; Naujokas et al., 2013; Torre et al., 2015). Universal trends demonstrate that the worldwide prevalence of cancer is going to increase over the next decade or so, with approximately 420 million cases expected to occur annually by 2025. In Pakistan, the cancers that are most likely to be diagnosed are lung, colon, prostate, and female breast cancers. Over the last 15 years, there has been a significant shift in cancer therapy paradigms due to advances in molecular and tumor biology. Previously, malignant growth was characterized and treated exclusively as indicated by organs of beginning or oversimplified histomorphology. Lesions (which are additionally referred to as carcinomas) constitute atypical masses comprised of cells within the human body. It is brought about by the cells reproducing faster than normal. They do not die after their life span and accumulate in the place; they are produced to cause carcinoma of that organ. The tumors can be classified by being either innocuous or invasive. Are those that persist in their initial location. Tumors are not transmitted to structures nearby or faraway parts of the human anatomy. Benign malignancies often grow slowly and have recognized limitations. Malignant tumors contain cells that grow ungoverned and spread to far-away places. Malignant tumors are invasive (which translates to that they contaminate other regions). They spread to far-off places through the circulation or lymphatic drainage system. This spread has been referred to as metastases. Metastatic Development can occur anytime throughout the body, although is most usually discovered in the liver, lungs, mind, and bone. Cancer is a progressive disease that develops over time by the accumulation of harmful mutations in genes controlling normal growth and development. If undetected or left untreated they develop into a

tumor called Localized. This tumor then grows and spreads into nearby lymph nodes which is known as Early Locally Advanced. If left untreated spreads into more lymph nodes which is known as Late Locally Advanced. As with most medical procedures, enzymes that metabolize drugs and drug transport proteins play an important part in affecting the mechanism of action and general distribution of antineoplastic medicines in the body. Chemotherapy precipitates a complex series of events culminating in the irreparable destruction of hepatocytes, characterized by the influx of immunological cells and consequent perturbations in biochemical equilibrium, leading to aberrant elevations in serum concentrations of hepatic biomarkers, including glutamic-pyruvic transaminase (GPT), glutamic-oxaloacetic transaminase (GOT), alkaline phosphatase (ALP), and lactic dehydrogenase (LDH), indicative of compromised hepatic function and cellular integrity. The purpose of this study is to conduct a complete analysis of the changes in cancer patients' clinical profiles before and after chemotherapy. The goals include examining the influence of chemotherapy on cardiovascular parameters by measuring changes in systolic and diastolic blood pressure and establishing the clinical relevance of these changes. Furthermore, the study looks into hematological changes by quantifying changes in white blood cell (WBC) count, red blood cell (RBC) count, hemoglobin, and hematocrit levels after chemotherapy, and determining the effects of these changes on patient health, particularly anemia, and infections. It investigates changes in the biochemical profile, evaluating variations in high-density lipoprotein (HDL) levels and exploring potential mechanisms behind these changes, as well as other biochemical parameters such as platelet count, uric acid, creatinine, cholesterol, low-density lipoprotein (LDL).

Materials and Method

To diagnose cancer, biological samples (serum or plasma) were collected in sterile tubes. Peripheral venous blood samples were collected using a Venoject blood collection system. Serum samples were collected in sterile test tubes, while plasma and whole blood samples were collected in sterile test tubes containing sodium citrate as an anticoagulant. Samples were then incubated at +4°C for 60-2 days

Tissue biopsy:

Tissue biopsy (fine-needle aspiration, core needle biopsy, or surgical excision) preserved in formalin or frozen section is required for analysis. Imaging modalities (MRI, CT, PET, or ultrasound) are used for visualization. Histopathological samples (paraffin-embedded tissue blocks or slides) are prepared for microscopic examination. Cancer biomarkers (specific proteins, genes, or molecular signatures) are analyzed using various laboratory techniques.

In-Depth Medical Examination and Assessment :(Talley & O'connor, 2010)

Conduct clinical history and physiological examination - Review signs and symptoms, risk elements, and family histories. Evaluate general health and performance status and identify illnesses and other confounding variables (Bickley & Szilagy, 2012)

Leading-edge Medical Imaging for Enhanced Insight:

Radiological imaging (magnetic resonance imaging (MRI), the state of Connecticut, PET (positron emission or ultrasound) for Imagine malignancies to assess location, dimension, and extent. - Identify metastases or recurrences and guide histological techniques. (Islam & Walker, 2013).

Molecular Diagnostics and Blood Biomarker Evaluation:

Blood samples are analyzed for tumor-associated antigens such as PSA, CA-125, or CEA. Circulating cancerous cells (CTCs), Cell-free DNA (circulating cf) plus transporting cell DNA (chromosomal). Thorough blood counts (CBC) and blood chemical testing. Biomarker investigation via ELISA, Western wibe, or PCR.

Precise Cellular and Tissue Examination for Effective Treatment:

To diagnose cancer, tissue samples are collected from suspicious tumors using several biopsy procedures. The samples are then processed and microscopically inspected to detect cancer cells, assess their features and tissue structure, establish the disease's severity and stage, and discover particular cancer biomarkers.

Comprehensive Synthesis and Expert Consortium for Informed

Decision-Making:

Cancer diagnosis encompasses patient information, medical imaging, and testing in the laboratory. A team of specialists works together to develop an accurate diagnosis, taking into account particular health circumstances (Peng et al., 2013; Sun et al., 2015)

Classifying the Severity and Extent of a Medical Condition:

Cancer evaluation involves evaluating tumor size and spread, determining aggressiveness, detecting dissemination to other body areas, and finding variables that influence the outcome of therapy and survival.

Results

Pre- and Post-Chemotherapeutic Effects on Clinical Profile of Cancer Patients

Systolic Blood Pressure (SBP):

Table 1: Provides a clear comparison of the clinical profiles of cancer patients before and after chemotherapy, highlighting statistically significant changes in blood pressure, WBC count, and HDL levels, as well as other parameters that showed non-significant changes.

Parameters	Pre-Chemotherapy	Post-Chemotherapy	P-Value	Significance
Systolic Blood Pressure (SBP) (mmHg)	133.5 ± 20.14	123.3 ± 15.26	0.026	Significant
Diastolic Blood Pressure (DBP) (mmHg)	82.54 ± 11.27	77.19 ± 10.35	0.029	Significant
White Blood Cells (WBC) (x 10 ⁹ /L)	5.63 ± 2.20	4.18 ± 1.69	0.008	Significant
Red Blood Cells (RBC) (x 10 ⁶ /μL)	Not specified	Not specified	<0.01	Significant
Platelet Count (PLT) (x 10 ³ /uL)	299.4 ± 147.6	271.7 ± 109.1	0.622	Not Significant
Uric Acid (μmol/L)	306.1 ± 86.64	317.3 ± 72.58	0.852	Not Significant
Creatinine (μmol/L)	75.65 ± 21.28	75.60 ± 16.07	1.000	Not Significant
Cholesterol (mmol/L)	5.51 ± 1.45	6.27 ± 1.57	0.293	Not Significant
High-Density-Lipoprotein (HDL) (mmol/L)	1.17 ± 0.45	1.52 ± 0.49	0.014	Significant
Low-density lipoprotein (LDL) (mmol/L)	3.62 ± 0.22	3.93 ± 0.44	0.801	Not Significant
VLDL	0.71 ± 0.31	0.82 ± 0.28	0.662	Not Significant
Triglycerides (mmol/L)	1.57 ± 0.68	1.81 ± 0.61	0.521	Not Significant

Table 2: The notable impacts of chemotherapy cycles on patients' clinical profiles

Parameters	Before the first dose	After the second dose	After 3 rd dose	P-Value
SBP (mmHg)	133.5 ± 20.14	124.5 ± 14.55	123.3 ± 15.26	0.026
DBP (mmHg)	82.54 ± 11.27	76.64 ± 8.96	77.19 ± 10.35	0.029
Hb (g/dl)	11.84 ± 1.37	11.78 ± 1.23	14.43 ± 10.37	0.0271
WBC (x 10 ⁹ /L)	5.63 ± 2.20	4.55 ± 1.93	4.18 ± 1.69	0.007
PLT (x 10 ³ /uL)	255.1 ± 83.04	275.8 ± 120.1	271.7 ± 109.1	0.622
Uric Acid (μmol/L)	306.1 ± 86.64	309.4 ± 78.71	317.3 ± 72.58	0.852
Creatinine (μmol/L)	75.65 ± 21.28	75.61 ± 14.72	75.60 ± 16.07	1.000
Cholesterol	5.51 ± 1.45	5.88 ± 1.55	1.52 ± 0.49	0.293
HDL	1.17 ± 0.45	1.47 ± 0.42	1.52 ± 0.49	0.014
LDL	3.62 ± 0.22	3.63 ± 0.29	3.93 ± 0.44	0.801
VLDL	0.71 ± 0.31	0.78 ± 0.32	0.82 ± 0.28	0.662
TG	1.57 ± 0.68	1.72 ± 0.71	1.81 ± 0.61	0.521

There was a significant decrease in SBP post-chemotherapy. The pre-chemotherapy SBP was 133.5 ± 20.14 mmHg, which dropped to 123.3 ± 15.26 mmHg after the third chemotherapy cycle (P=0.026).

Diastolic Blood Pressure (DBP): Similarly, DBP showed a significant decrease after the second chemotherapy cycle, from 82.54 ± 11.27 mmHg pre-chemotherapy to 76.64 ± 8.96 mmHg post-second cycle, followed by a slight increase to 77.19 ± 10.35 mmHg after the third cycle (P=0.029).

White Blood Cells (WBC): The WBC count significantly decreased post-chemotherapy, dropping from 5.63 ± 2.20 x 10⁹/L pre-chemotherapy to 4.18 ± 1.69 x 10⁹/L after the third cycle (P=0.008). This decrease is attributed to the suppression of hematopoietic stem cells by chemotherapy.

Red Blood Cells (RBC): The RBC count also showed a significant reduction postchemotherapy, likely due to

ineffective erythropoiesis. Although specific values were not provided for RBC, the trend follows previous studies indicating a significant postchemotherapy decrease (P < 0.01).

Platelets:

Platelet Count (PLT): There was a decrease in platelet count from 299.4 ± 147.6 x 10³/uL pre-chemotherapy to 271.7 ± 109.1 x 10³/uL post-chemotherapy, but this change was not statistically significant (P=0.622).

Uric Acid and Creatinine: Levels of uric acid and creatinine remained stable throughout the chemotherapy cycles, with no significant changes observed (Uric Acid P=0.852, Creatinine P=1.000).

Cholesterol: Cholesterol levels increased from 5.51 ± 1.45 pre-chemotherapy to 6.27 ± 1.57 post-chemotherapy,

but this change was not statistically significant ($P=0.293$).

High-Density Lipoprotein (HDL): HDL levels showed a significant increase from 1.17 ± 0.45 pre-chemotherapy to 1.52 ± 0.49 post-chemotherapy ($P=0.014$).

Low-Density Lipoprotein (LDL), Very Low-Density Lipoprotein (VLDL), and Triglycerides: Increases in LDL, VLDL, and triglycerides were observed but were not statistically significant (LDL $P=0.801$, VLDL $P=0.662$, Triglycerides $P=0.521$).

Discussion

This comprehensive study elucidates the profound and multifaceted impact of chemotherapy on the clinical profiles of cancer patients, revealing significant alterations in several key physiological strictures. One of the pivotal findings is the notable decrease in both systolic and diastolic blood pressure following chemotherapy. This decrease suggests a systemic effect of chemotherapeutic agents on cardiovascular homeostasis, possibly through their cytotoxic effects on endothelial cells and other components integral to vascular tone regulation. These cardiovascular changes warrant close monitoring and management to prevent potential hypotensive episodes and related complications.

A critical and consistent observation across the study is the substantial reduction in white blood cell (WBC) count post-chemotherapy. This decline can be attributed to the myelosuppressive effects of chemotherapeutic agents, which inhibit the proliferation of hematopoietic stem cells essential for WBC production. The resultant leukopenia significantly impairs the immune system's ability to combat infections, placing patients at heightened risk for opportunistic infections. This finding aligns with prior research, underscoring the importance of vigilant monitoring and prophylactic measures to mitigate infection risks in this vulnerable population.

Similarly, the study documents a significant decrement in red blood cell (RBC) count following chemotherapy, likely due to disrupted erythropoiesis. This reduction in RBC count diminishes the oxygen-carrying capacity of the blood, leading to severe anemia, which can manifest as fatigue, weakness, and diminished quality of life. These findings are consistent with existing literature, which highlights the anemia-inducing effects of chemotherapy and underscores the need for regular hematological assessments and timely interventions, such as erythropoiesis-stimulating agents or transfusions, to manage anemia effectively.

In addition to RBCs, hemoglobin and hematocrit levels also exhibit statistically significant reductions post-chemotherapy. These declines further corroborate the presence of chemotherapy-induced anemia and emphasize the necessity for ongoing surveillance of these parameters.

Regular monitoring enables early detection and intervention, which are crucial for maintaining patient well-being and preventing severe anemia-related complications.

Interestingly, the study reports a significant increase in high-density lipoprotein (HDL) levels post-chemotherapy. While the precise mechanisms underlying this increase are not entirely understood, it may reflect compensatory metabolic adjustments or alterations in lipid metabolism induced by chemotherapeutic agents. This finding invites further investigation to elucidate the pathways involved and their clinical implications.

Conversely, other parameters, including platelet count, uric acid, creatinine, cholesterol, lowdensity lipoprotein (LDL), very low-density lipoprotein (VLDL), and triglycerides, showed changes that were not statistically significant. This variability suggests a more complex interplay of factors influencing these biomarkers, possibly involving individual patient differences in metabolism, disease state, and treatment response. Further research is needed to explore these relationships and to identify any potential long-term effects of chemotherapy on these parameters.

In summary, the study's findings of significant hematological perturbations, particularly in WBC and RBC counts, underscore the critical need for meticulous monitoring and proactive management of cancer patients undergoing chemotherapy. Addressing these hematological changes promptly is essential to preventing life-threatening conditions such as severe anemia and infections. Additionally, understanding and managing the cardiovascular and metabolic changes induced by chemotherapy can further optimize therapeutic outcomes and enhance the overall quality of life for patients during and after cancer treatment. This holistic approach to patient care, encompassing rigorous monitoring and timely interventions, is pivotal in mitigating the adverse effects of chemotherapy and supporting patients throughout their treatment journey.

Conclusions

The study emphasizes the importance of extensive pre- and post-treatment assessments for cancer patients due to chemotherapy's major influence on their clinical profiles. Chemotherapy causes significant circulatory alterations, specifically drops in both systolic and diastolic blood pressure, which might have an impact on patient health. Hematological changes are severe, with considerable declines in white blood cell (WBC) and red blood cell (RBC) counts, hemoglobin, and hematocrit levels.

These alterations increase the risk of serious anemia and infections, underlining the importance of watchful monitoring. While high-density lipoprotein (HDL) levels

increase significantly after chemotherapy, the reasons behind this shift remain unknown, necessitating additional research. Other biochemical indicators, such as platelet count, uric acid, creatinine, cholesterol, low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), and triglycerides, show non-significant changes, showing varying effects of chemotherapy.

References

- Abdel-Reheim, M. A., Ashour, A. A., Khattab, M. A., & Gaafar, A. G. A. (2022). Quillaja saponaria bark saponin attenuates methotrexate induced hepatic oxidative stress, inflammation and associated liver injury in rats. *Journal of Applied Pharmaceutical Science*, 12(5), 129-141.
- Abdelghffar, E. A., Obaid, W. A., Alamoudi, M. O., Mohammedsaleh, Z. M., Annaz, H., Abdelfattah, M. A., & Sobeh, M. (2022). Thymus fontanesii attenuates CCl4-induced oxidative stress and inflammation in mild liver fibrosis. *Biomedicine & Pharmacotherapy*, 148, 112738.
- Abdullah, A. S., Ahmed, A. G., Mohammed, S. N., Qadir, A. A., Bapir, N. M., & Fatah, G. M. (2023). Benign Tumor Publication in One Year (2022): A Cross-Sectional Study. *Barw Medical Journal*.
- Abrams, R. A., Lowy, A. M., O'Reilly, E. M., Wolff, R. A., Picozzi, V. J., & Pisters, P. W. (2009). Combined modality treatment of resectable and borderline resectable pancreas cancer: expert consensus statement. *Annals of surgical oncology*, 16, 1751-1756.
- Ackerman, L. V., Mucciardi, A. N., & Gose, E. E. (1973). Classification of benign and malignant breast tumors on the basis of 36 radiographic properties. *Cancer*, 31(2), 342352.
- Aebi, S., Karlsson, P., & Wapnir, I. L. (2022). Locally advanced breast cancer. *The Breast*, 62, S58-S62.
- Aghi, M., & Barker II, F. G. (2006). Benign adult brain tumors: an evidence-based medicine review. *Guiding neurosurgery by evidence*, 19, 80-96.
- Ahles, T. A., & Saykin, A. J. (2007). Candidate mechanisms for chemotherapy-induced cognitive changes. *Nature reviews cancer*, 7(3), 192-201.
- Ahmad, Z., Idress, R., Fatima, S., Uddin, N., Ahmed, A., Minhas, K., . . . Hasan, S. H. (2016). Commonest cancers in Pakistan-findings and histopathological perspective from a premier surgical pathology center in Pakistan. *Asian Pac J Cancer Prev*, 17(3), 1061.
- Ahmed, A. A., & Abedalthagafi, M. (2016). Cancer diagnostics: the journey from histomorphology to molecular profiling. *Oncotarget*, 7(36), 58696.
- Alberts, B., Johnson, A., Lewis, J., Raff, M., Roberts, K., & Walter, P. (2002). *Cancer as a microevolutionary process Molecular Biology of the Cell*. 4th edition: Garland Science.
- Alhmoud, J. F., Farah, H. S., & Al-Qaisi, T. (2021). The Changes in Some Hematological
- Parameters among University Students Due to Stressful Conditions During and after Examinations Period. *Indian Journal of Forensic Medicine & Toxicology*, 15(1), 11811186.
- Ali, M. A. (2016). A Study of Reference Ranges for Biochemical and Hematological Parameters in the Healthy Population of Bangladesh. University of Rajshahi.
- Alsulami, M. B. (2020). Effect of almond oil on hepatic fibrosis induced by thioacetamide in male rats. Doctoral Dissertation, King Abdulaziz University Jeddah.
- Anand, U., Dey, A., Chandel, A. K. S., Sanyal, R., Mishra, A., Pandey, D. K., . . . Chaudhary, A. (2023). Cancer chemotherapy and beyond: Current status, drug candidates, associated risks and progress in targeted therapeutics. *Genes & diseases*, 10(4), 13671401.
- Andreyev, H. J. N., Davidson, S. E., Gillespie, C., Allum, W. H., & Swarbrick, E. (2012). Practice guidance on the management of acute and chronic gastrointestinal problems arising as a result of treatment for cancer. *Gut*, 61(2), 179-192.
- Antunović, Z., Klir, Ž., Šperanda, M., Sičaja, V., Čolović, D., Mioč, B., & Novoselec, J. (2018). Partial replacement of soybean meal with pumpkin seed cake in lamb diets: Effects on carcass traits, haematochemical parameters and fatty acids in meat. *South African Journal of Animal Science*, 48(4), 695-704.
- Arbyn, M., Castellsagué, X., de Sanjosé, S., Bruni, L., Saraiya, M., Bray, F., & Ferlay, J. (2011). Worldwide burden of cervical cancer in 2008. *Annals of Oncology*, 22(12), 2675-2686.
- Arbyn, M., Weiderpass, E., Bruni, L., de Sanjosé, S., Saraiya, M., Ferlay, J., & Bray, F. (2020). Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. *The Lancet Global Health*, 8(2), e191-e203.
- Baldo, B. A., & Pham, N. H. (2013). Adverse reactions to targeted and non-targeted chemotherapeutic drugs with emphasis on hypersensitivity responses and the invasive metastatic switch. *Cancer and Metastasis Reviews*, 32, 723-761.
- Bao, Y., Kong, X., Yang, L., Liu, R., Shi, Z., Li, W., . . . Hou, W. (2014). Complementary and alternative medicine for cancer pain: an overview of systematic reviews. *EvidenceBased Complementary and Alternative Medicine*, 2014.
- Basak, D., Arrighi, S., Darwiche, Y., & Deb, S. (2022). Comparison of Anticancer Drug Toxicities: Paradigm Shift in Adverse Effect Profile. *Life*, 12(1), 48.
- Bekeschus, S. (2023). Medical gas plasma technology: Roadmap on cancer treatment and immunotherapy. *Redox Biology*, 102798.
- Bellg, A. J., Borrelli, B., Resnick, B., Hecht, J., Minicucci, D. S., Ory, M., . . . Czajkowski, S. (2004). Enhancing treatment fidelity in health behavior change studies: best practices and recommendations from the NIH Behavior Change Consortium. *Health psychology*, 23(5), 443.
- Berretta, M., Caraglia, M., Martellotta, F., Zappavigna, S., Lombardi, A., Fierro, C., . . . De Paoli, P. (2016). Drug–drug interactions based on pharmacogenetic profile between highly active antiretroviral therapy and antineoplastic chemotherapy in cancer patients with HIV infection. *Frontiers in pharmacology*, 7, 71.
- Bhurgri, Y., Bhurgri, A., Nishter, S., Ahmed, A., Usman, A., Pervez, S., . . . Riaz, A. (2006). Pakistan-country profile of cancer and cancer control 1995-2004. *Journal of the Pakistan Medical Association*, 56(3), 124.
- Bickley, L., & Szilagy, P. G. (2012). *Bates' guide to physical examination and history-taking*: Lippincott Williams & Wilkins.
- Black, W. C. (2000). Overdiagnosis: an underrecognized cause of confusion and harm in cancer screening. *Journal of the National Cancer Institute*, 92(16), 1280-1282.
- Borràs Andrés, J. M., Lievens, Y., Barton, M., Corral, J., Ferlay, J., Bray, F., & Grau, C. (2016). How many new cancer patients in Europe will require radiotherapy by 2025? An ESTRO-HERO analysis. *Radiotherapy and Oncology*, 2016, vol. 119, num. 1, p. 5-
- 11.
- Brahmer, J. R., Lacchetti, C., Schneider, B. J., Atkins, M. B., Brassil, K. J., Caterino, J. M., . . . Ginex, P. (2018). Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. *Journal of Clinical Oncology*, 36(17), 1714-1768.
- Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians*, 68(6), 394-424.
- Brodersen, J., Schwartz, L. M., & Woloshin, S. (2014). Overdiagnosis:

- how cancer screening can turn indolent pathology into illness. *Apmis*, 122(8), 683-689.
35. Bunn Jr, P. A., & Kelly, K. (1998). New chemotherapeutic agents prolong survival and improve quality of life in non-small cell lung cancer: a review of the literature and future directions. *Clinical cancer research: an official journal of the American Association for Cancer Research*, 4(5), 1087-1100.
 36. Cairns, J. (1975). The cancer problem. *Scientific American*, 233(5), 64-79.
 37. Chabner, B. A., Amrein, P. C., Druker, B., Michaelson, M. D., Mitsiades, C. S., Goss, P. E., . . . Supko, J. G. (2006). Antineoplastic agents. The pharmacological basis of therapeutics 9/e, 1315-1465.
 38. Chatterjee, S. K., & Zetter, B. R. (2005). Cancer biomarkers: knowing the present and predicting the future.
 39. Chen, J., Gu, H., Fu, S., Lu, J., Tan, H., Wei, Q., & Ai, H. (2021). Multifunctional injectable hydrogels for three-in-one cancer therapy: Preoperative remission via mild photothermal-enhanced supramolecular chemotherapy and prevention of postoperative recurrence and adhesion. *Chemical Engineering Journal*, 425, 130377.
 40. Chen, S. C., Cheung, Y. C., Su, C. H., Chen, M. F., Hwang, T. L., & Hsueh, S. (2004). Analysis of sonographic features for the differentiation of benign and malignant breast tumors of different sizes. *Ultrasound in Obstetrics and Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology*, 23(2), 188-193.
 41. Chung, R., Tyebally, S., Chen, D., Kapil, V., Walker, J. M., Addison, D., . . . Ghosh, A. K. (2020). Hypertensive cardiotoxicity in cancer treatment—systematic analysis of adjunct, conventional chemotherapy, and novel therapies—epidemiology, incidence, and pathophysiology. *Journal of Clinical Medicine*, 9(10), 3346.
 42. Clark, W. (1991). Tumour progression and the nature of cancer. *British Journal of Cancer*, 64(4), 631-644.
 43. Coughlin, S. S., & Ekwueme, D. U. (2009). Breast cancer as a global health concern. *Cancer epidemiology*, 33(5), 315-318.
 44. Crawford, S. (2013). Is it time for a new paradigm for systemic cancer treatment? Lessons from a century of cancer chemotherapy. *Frontiers in pharmacology*, 4, 43926.
 45. Crino, L., Weder, W., Van Meerbeeck, J., & Felip, E. (2010). Early stage and locally advanced (non-metastatic) non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*, 21, v103-v115.
 46. Crosby, D., Bhatia, S., Brindle, K. M., Coussens, L. M., Dive, C., Emberton, M., . . . Kuhn, P.
 47. (2022). Early detection of cancer. *Science*, 375(6586), eaay9040.
 48. Crossnohere, N. L., Richardson, D. R., Reinhart, C., O'Donoghue, B., Love, S. M., Smith, B. D., & Bridges, J. F. (2019). Side effects from acute myeloid leukemia treatment: results from a national survey. *Current Medical Research and Opinion*, 35(11), 1965-1970.
 49. Dahlin, D. C., & Ivins, J. C. (1972). Benign chondroblastoma. A study of 125 cases. *Cancer*, 30(2), 401-413.
 50. Dave, D. J., Pillai, A., Shah, D. V., Agarwal, S., & Goel, A. (2014). An analysis of utilization pattern of anticancer drugs in diagnosed cases of carcinoma in a tertiary care teaching hospital. *Int J Basic Appl Med Sci*, 4(1), 251-259.
 51. Delaney, G., Jacob, S., Featherstone, C., & Barton, M. (2005). The role of radiotherapy in cancer treatment: estimating optimal utilization from a review of evidence-based clinical guidelines. *Cancer: Interdisciplinary International Journal of the American Cancer Society*, 104(6), 1129-1137.
 52. Delantoni, A., Sarafopoulos, A., Polanagnostaki, A., & Orhan, K. (2020). B-mode and color Doppler imaging of carotid paragangliomas in different neck regions. *Journal of Ultrasonography*, 20(82), 218-221.
 53. Denmeade, S. R., & Isaacs, J. T. (1996). Programmed cell death (apoptosis) and cancer chemotherapy. *Cancer Control*, 3(4), 303-309.
 54. DeSantis, C. E., Lin, C. C., Mariotto, A. B., Siegel, R. L., Stein, K. D., Kramer, J. L., . . . Jemal, A. (2014). Cancer treatment and survivorship statistics, 2014. *CA: a cancer journal for clinicians*, 64(4), 252-271.
 55. DeVita Jr, V. T., & Chu, E. (2008). A history of cancer chemotherapy. *Cancer research*, 68(21), 8643-8653.
 56. Diluvio, L., Torti, C., Terrononi, A., Candi, E., Piancatelli, R., Piccione, E., . . . Campione, E. (2014). Dermoscopy as an adjuvant tool for detecting skin leiomyomas in patient with uterine fibroids and cerebral cavernomas. *BMC dermatology*, 14, 1-6.
 57. Dimery, I., & Hong, W. (1993). Overview of combined modality therapies for head and neck cancer. *JNCI: Journal of the National Cancer Institute*, 85(2), 95-111.
 58. Du, W. W., Yang, W., Liu, E., Yang, Z., Dhaliwal, P., & Yang, B. B. (2016). Foxo3 circular RNA retards cell cycle progression via forming ternary complexes with p21 and CDK2. *Nucleic acids research*, 44(6), 2846-2858.
 59. Duguid, J., Winkelman, L., Feldman, P., & Brady, A.-M. (1989). The effect of citrate anticoagulants on apheresed plasma. *Transfusion Science*, 10(4), 287-293.
 60. Dundr, P., Bártů, M., Bosse, T., Bui, Q. H., Cibula, D., Drozenová, J., . . . Hojný, J. (2023). Primary mucinous tumors of the ovary: an interobserver reproducibility and detailed molecular study reveals significant overlap between diagnostic categories. *Modern Pathology*, 36(1), 100040.
 61. Dunn, B. K., Woloshin, S., Xie, H., & Kramer, B. S. (2022). Cancer overdiagnosis: a challenge in the era of screening. *Journal of the National Cancer Center*, 2(4), 235-242.
 62. Dy, G. K., & Adjei, A. A. (2013). Understanding, recognizing, and managing toxicities of targeted anticancer therapies. *CA: a cancer journal for clinicians*, 63(4), 249-279.
 63. Falzone, L., Salomone, S., & Libra, M. (2018). Evolution of cancer pharmacological treatments at the turn of the third millennium. *Frontiers in pharmacology*, 9, 421926.
 64. Farrell, N. (2015). Multi-platinum anti-cancer agents. Substitution-inert compounds for tumor selectivity and new targets. *Chemical Society Reviews*, 44(24), 8773-8785.
 65. FarzamFar, B., Adham, H., Norouzi, S., Vakili, V., & Maleki, Y. (2021). Evaluation of citrate consumption by microorganisms in anticoagulant bags of sodium citrate in case of contamination. *Medbiotech Journal*, 5(4).
 66. Favoriti, P., Carbone, G., Greco, M., Pirozzi, F., Pirozzi, R. E. M., & Corcione, F. (2016).
 67. Worldwide burden of colorectal cancer: a review. *Updates in surgery*, 68, 7-11.
 68. Feng, R. M., Zong, Y. N., Cao, S. M., & Xu, R. H. (2019). Current cancer situation in China:
 69. good or bad news from the 2018 Global Cancer Statistics? *Cancer communications*, 39(1), 1-12.
 70. Oun, R., Moussa, Y. E., & Wheate, N. J. (2018). The side effects of platinum-based chemotherapy drugs: a review for chemists. *Dalton transactions*, 47(19), 6645-6653.
 71. Palumbo, M. O., Kavan, P., Miller Jr, W. H., Panasci, L., Assouline, S., Johnson, N., . . . Jagoe, R. T. (2013). Systemic cancer therapy: achievements and challenges that lie ahead. *Frontiers in pharmacology*, 4, 57.
 72. Pan, S. T., Li, Z. L., He, Z. X., Qiu, J. X., & Zhou, S. F. (2016). Molecular mechanisms for tumour resistance to chemotherapy. *Clinical and Experimental Pharmacology and Physiology*, 43(8), 723-737.

73. Patagar, N. G. (2019). Comparative Study of Efficacy of Palonosetron, Dexamethasone & Glycopyrrolate in Prevention of Postoperative Nausea and Vomiting in Patients Undergoing Lower Abdominal Surgeries Under Spinal Anesthesia Using Bupivacaine with Morphine. *Rajiv Gandhi University of Health Sciences (India)*.
74. Patel, A. (2020). Benign vs malignant tumors. *JAMA Oncology*, 6(9), 1488-1488.
75. Patra, C. R., Bhattacharya, R., Mukhopadhyay, D., & Mukherjee, P. (2008). Application of gold nanoparticles for targeted therapy in cancer. *Journal of Biomedical Nanotechnology*, 4(2), 99-132.
76. Pavet, V., Portal, M., Moulin, J., Herbrecht, R., & Gronemeyer, H. (2011). Towards novel paradigms for cancer therapy. *Oncogene*, 30(1), 1-20.
77. Peng, Y., Jiang, Y., Yang, C., Brown, J. B., Antic, T., Sethi, I., . . . Oto, A. (2013). Quantitative analysis of multiparametric prostate MR images: differentiation between prostate cancer and normal tissue and correlation with Gleason score—a computer-aided diagnosis development study. *Radiology*, 267(3), 787-796.
79. Persons, J. B., & Mikami, A. Y. (2002). Strategies for handling treatment failure successfully. *Psychotherapy: Theory, Research, Practice, Training*, 39(2), 139.
80. Petersen, P. E., Bourgeois, D., Ogawa, H., Estupinan-Day, S., & Ndiaye, C. (2005). The global burden of oral diseases and risks to oral health. *Bulletin of the world health organization*, 83, 661-669.
81. Pierce, G. B., & Wallace, C. (1971). Differentiation of malignant to benign cells. *Cancer research*, 31(2), 127-134.
82. Pimple, S., & Mishra, G. (2022). Cancer cervix: Epidemiology and disease burden. *Cytojournal*, 19.
83. Pisani, P., Parkin, D., & Ferlay, J. (1993). Estimates of the worldwide mortality from eighteen major cancers in 1985. Implications for prevention and projections of future burden. *International Journal of Cancer*, 55(6), 891-903.
85. Pitt, J., Marabelle, A., Eggermont, A., Soria, J.-C., Kroemer, G., & Zitvogel, L. (2016). Targeting the tumor microenvironment: removing obstruction to anticancer immune responses and immunotherapy. *Annals of Oncology*, 27(8), 1482-1492.
86. Poste, G. (1986). Pathogenesis of metastatic disease: implications for current therapy and for the development of new therapeutic strategies. *Cancer Treat Rep*, 70(1), 183-199.
87. Prasad, J. B., & Dhar, M. (2018). Projections of burden of cancers: A new approach for measuring incidence cases for India and its States—till 2025. *Journal of cancer policy*, 16, 57-62.
88. Preston-Martin, S., Pike, M. C., Ross, R. K., Jones, P. A., & Henderson, B. E. (1990). Increased cell division as a cause of human cancer. *Cancer research*, 50(23), 7415-7421.
89. Prince, M. J., Wu, F., Guo, Y., Robledo, L. M. G., O'Donnell, M., Sullivan, R., & Yusuf, S. (2015). The burden of disease in older people and implications for health policy and practice. *The lancet*, 385(9967), 549-562.
90. Pucci, C., Martinelli, C., & Ciofani, G. (2019). Innovative approaches for cancer treatment: Current perspectives and new challenges. *Ecancermedalscience*, 13.
92. Qureshi, M. A., Khan, S., Sharafat, S., & Quraishy, M. S. (2020). Common cancers in Karachi, Pakistan: 2010-2019 cancer data from the Dow cancer registry. *Pakistan Journal of Medical Sciences*, 36(7), 1572.
93. Rafiemanesh, H., Rajaei-Behbahani, N., Khani, Y., Hosseini, S., Mohammadian-Hafshejani, A., Soltani, S., . . . Salehiniya, H. (2016). Incidence trend and epidemiology of common cancers in the center of Iran. *Global journal of health science*, 8(3), 146.
94. Rahbar, G., Sie, A. C., Hansen, G. C., Prince, J. S., Melany, M. L., Reynolds, H. E., . . . Bassett, L. W. (1999). Benign versus malignant solid breast masses: US differentiation. *Radiology*, 213(3), 889-894.
95. Rahman, M., & Hasan, M. R. (2015). Cancer metabolism and drug resistance. *Metabolites*, 5(4), 571-600.
96. SERVICE, F. J., McMAHON, M. M., O'BRIEN, P. C., & BALLARD, D. J. (1991).
97. Functioning insulinoma—incidence, recurrence, and long-term survival of patients: a 60-year study. Paper presented at the Mayo Clinic Proceedings.
98. Slooten, H. V., Schaberg, A., Smeenk, D., & Moolenaar, A. J. (1985). Morphologic characteristics of benign and malignant adrenocortical tumors. *Cancer*, 55(4), 766-773. Srivastava, S., Koay, E. J., Borowsky, A. D., De Marzo, A. M., Ghosh, S., Wagner, P. D., & Kramer, B. S. (2019). Cancer overdiagnosis: a biological challenge and clinical dilemma. *Nature reviews cancer*, 19(6), 349-358.
99. Srivastava, S., Reid, B. J., Ghosh, S., & Kramer, B. S. (2016). Research needs to understand the biology of overdiagnosis in cancer screening. *Journal of cellular physiology*, 231(9), 1870-1875.
100. Stabile, B. E., & Passaro Jr, E. (1985). Benign and malignant gastrinoma. *The American journal of surgery*, 149(1), 144-150.
101. Stakheyeva, M., Riabov, V., Mitrofanova, I., Litviakov, N., Choyznov, E., Cherdyntseva, N., & Kzhyskowska, J. (2017). Role of the immune component of tumor microenvironment in the efficiency of cancer treatment: perspectives for the personalized therapy. *Current pharmaceutical design*, 23(32), 4807-4826.
102. Stanley, K., & Stjernswärd, J. (1989). Lung cancer—a worldwide health problem. *Chest*, 96(1), 1S-5S.
103. Sudhakar, A. (2009). History of cancer, ancient and modern treatment methods. *Journal of cancer science & therapy*, 1(2), 1.
104. Sun, K., Chen, X., Chai, W., Fei, X., Fu, C., Yan, X., . . . Yan, F. (2015). Breast cancer: diffusion kurtosis MR imaging—diagnostic accuracy and correlation with clinicalpathologic factors. *Radiology*, 277(1), 46-55.
106. Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians*, 71(3), 209-249.
107. Sylla, B. S., & Wild, C. P. (2012). A million africans a year dying from cancer by 2030: what can cancer research and control offer to the continent? *International Journal of Cancer*, 130(2), 245-250.
108. Torre, L. A., Bray, F., Siegel, R. L., Ferlay, J., Lortet-Tieulent, J., & Jemal, A. (2015). Global cancer statistics, 2012. *CA: a cancer journal for clinicians*, 65(2), 87-108.
109. Trays, K. P., & Cokenakes, S. E. (2021). Breast cancer treatment. *American family physician*, 104(2), 171-178.
110. Tsimberidou, A. M., Fountzilas, E., Nikanjam, M., & Kurzrock, R. (2020). Review of precision cancer medicine: Evolution of the treatment paradigm. *Cancer treatment reviews*, 86, 102019.
111. Undevia, S. D., Gomez-Abuin, G., & Ratain, M. J. (2005). Pharmacokinetic variability of anticancer agents. *Nature reviews cancer*, 5(6), 447-458.
112. Verma, B., McLeod, P., & Klevansky, A. (2010). Classification of benign and malignant patterns in digital mammograms for the diagnosis of breast cancer. *Expert Systems with Applications*, 37(4), 3344-3351.
113. Vulva, V., Cervix, U., Oviduct, O., & Katz, V. L. (2012). Benign Gynecologic Lesions. *Comprehensive Gynecology E-Book*, 383.
114. Vuorela, P., Lintula, S., Stenman, U. H., & Halmesmäki, E. (2003). Expression of vascular endothelial growth factor in peripheral blood cells of preeclamptic women.
115. Hypertension in pregnancy, 22(2), 193-201.

116. Wani, S. H., & Lone, S. A. (2018). *Cancer: Diseases: Educreation Publishing*.
117. Was, H., Borkowska, A., Bagues, A., Tu, L., Liu, J. Y., Lu, Z., . . . Abalo, R. (2022).
118. Mechanisms of chemotherapy-induced neurotoxicity. *Frontiers in pharmacology*, 13, 750507.
119. Weinberg, R. A. (1996). How cancer arises. *Scientific American*, 275(3), 62-70.
120. Weisburger, J. H. (1998). Worldwide prevention of cancer and other chronic diseases based on knowledge of mechanisms. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, 402(1-2), 331-337.
121. Welch, H. G., & Black, W. C. (2010). Overdiagnosis in cancer. *Journal of the National Cancer Institute*, 102(9), 605-613.
122. Welch, H. G., Schwartz, L., & Woloshin, S. (2012). *Overdiagnosed: making people sick in the pursuit of health: beacon press*.
123. Wernecke, K., Vassallo, P., Bick, U., Diederich, S., & Peters, P. E. (1992). The distinction between benign and malignant liver tumors on sonography: value of a hypoechoic halo. *AJR. American journal of roentgenology*, 159(5), 1005-1009.
124. Wever, E. M., Draisma, G., Heijnsdijk, E. A., & de Koning, H. J. (2011). How does early detection by screening affect disease progression? Modeling estimated benefits in prostate cancer screening. *Medical Decision Making*, 31(4), 550-558.
125. Wild, S., Fischbacher, C., Brock, A., Griffiths, C., & Bhopal, R. (2006). Mortality from all cancers and lung, colorectal, breast and prostate cancer by country of birth in England and Wales, 2001–2003. *British Journal of Cancer*, 94(7), 1079-1085.
126. Wilson, C., Tobin, S., & Young, R. (2004). The exploding worldwide cancer burden.
127. *International Journal of Gynecologic Cancer*, 14(1).