HIGH SCHOOL EDITION
Journal of Student Research
Volume 12 Issue 4 (2023)

Interventions to Mitigate Chemotherapy Side Effects in Lung Cancer Patients

Wenlu Li

St. Andrew's School

ABSTRACT

Lung cancer remains a formidable challenge in oncology, necessitating innovative and comprehensive therapeutic approaches. Lung cancer treatment encompasses diverse modalities such as chemotherapy, radiotherapy, targeted therapy, and immunotherapy. Chemotherapy continues to stand as a fundamental treatment approach, yet the consequential side effects it brings forth pose significant barriers to its broad implementation and serve as a primary impediment in clinical practice. This review presents a detailed exploration of natural molecules, dietary strategies, and their potential to enhance chemotherapy's efficacy and mitigate adverse effects. Moreover, the significance of combined therapies emerges, elucidating their capacity to synergistically combat lung cancer through enhanced treatment efficacy, resistance prevention, and personalized patient care. This paper also underscores the value of adjuvant therapy and its role in extending patient survival and reducing recurrence rates. In addition, the interplay between gut microbiota and chemotherapy outcomes is examined, emphasizing the potential for microbiota modulation to optimize treatment responses. Conclusively, this comprehensive review underscores the dynamic landscape of lung cancer treatment, advocating for a holistic approach that integrates cutting-edge therapeutic paradigms to enhance patient outcomes and quality of life.

1. Introduction

Lung cancer is one of the most common cancers worldwide. The incidence of lung cancer varies geographically and is strongly associated with tobacco smoking, which is a major risk factor for the disease. Lung cancer has a high mortality rate, largely due to its often advanced stage at the time of diagnosis. The overall survival rate for lung cancer is relatively low, with a five-year survival rate around 20% (Thandra, Barsouk, Saginala, Aluru, & Barsouk, 2021). Lung cancer is broadly categorized into two main histological types: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC accounts for the majority of lung cancer cases (around 85%), with adenocarcinoma, squamous cell carcinoma, and large cell carcinoma being the major subtypes. SCLC, although less common, is more aggressive and tends to metastasize rapidly. Notably, SCLC is recognized for its aggressive nature and strong correlation with smoking habits. The hallmark symptoms of lung cancer encompass persistent coughing (often accompanied by blood), unexplained weight loss, breathlessness, and chest discomfort (Inamura, 2017; Lemjabbar-Alaoui, Hassan, Yang, & Buchanan, 2015).

While a spectrum of therapeutic options exists, chemotherapy remains the cornerstone of treatment (Hirsch et al., 2017). However, the substantial burden of chemotherapy-induced side effects poses considerable challenges to its application in cancer patients. Of particular concern is the potential long-term detriment inflicted by chemotherapy, which poses risks to post-treatment well-being (Henry et al., 2008). Consequently, the identification and implementation of strategies to ameliorate chemotherapy's adverse effects are imperative.

In this review, I will firstly give a comprehensive introduction on lung cancer biology, pathology and current therapies. Then my focus revolves around the assessment of interventions that have exhibited notable efficacy in mitigating the adverse effects of chemotherapy. By analyzing established approaches, I aim to glean insights into their

practical applicability and potential limitations. Furthermore, I will try to offer novel avenues to enhance the tolerability of chemotherapy and improve the overall quality of life for lung cancer patients.

2. Lung Cancer Progression and Therapeutic Advances

2.1 The Development of Lung Cancer

Lung cancer advances through intricate genetic and cellular transformations that disrupt the usual lung tissue regulation. Carcinogen exposure, primarily from smoking or environmental sources like radon or asbestos, triggers genetic mutations in lung cell DNA. These mutations induce uncontrolled cell growth and division. Mutated cells replicate to form genetically identical clusters known as clones, dividing faster and forming small tumors. Additional genetic changes hinder regular cellular processes, like apoptosis and DNA repair, allowing mutated cells to elude natural growth controls (Cooper, Lam, O'Toole, & Minna, 2013).

As the tumor enlarges, it requires a blood supply for sustenance. Tumor cells release angiogenic factors, promoting new blood vessel growth (angiogenesis) from nearby tissue. The tumor can infiltrate neighboring tissues and structures, potentially spreading to lung tissue and lymph nodes. Cancer cells can eventually detach from the primary tumor, entering the bloodstream or lymphatics, leading to distant metastasis. Lung cancer frequently metastasizes to organs such as the liver, bones, brain, and adrenal glands. The tumor microenvironment, consisting of immune cells, fibroblasts, blood vessels, and other elements, significantly influences tumor progression. Cancer cells manipulate this environment to enhance their survival, growth, and invasion. Over time, lung cancer cells may develop resistance to treatments like chemotherapy, targeted therapy, and immunotherapy, stemming from additional genetic mutations or tumor cell adaptations (Birring & Peake, 2005; Nooreldeen & Bach, 2021).

Small Cell Lung Cancer (SCLC) and Non-Small Cell Lung Cancer (NSCLC) are the two primary forms of lung cancer (Thandra et al., 2021). SCLC, accounting for about 15% of cases, is aggressive, often linked to smoking, and tends to metastasize rapidly. NSCLC, comprising approximately 85% of cases, includes subtypes like adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. NSCLC generally grows more slowly, and while smoking is a risk factor, it also occurs in non-smokers. SCLC responds well to initial treatment but has a poorer prognosis, whereas NSCLC has varied responses and prognoses depending on subtype, stage, and treatment. Overall, SCLC is known for its aggressiveness and early metastasis, while NSCLC is more diverse, often detected at different stages, and has a broader range of treatment options and outcomes. Liver metastasis is prevalent in SCLC, while brain metastasis occurs in both SCLC and adenocarcinoma. For non-small cell lung cancer (NSCLC), surgery is often pursued in early stages for potential cure. However, post-resection, a significant portion of NSCLC patients still face recurrence risks. While the 5-year survival rate after resection is promising for stage I patients, it drops to 25% for stage IIIA patients (Giaccone & He, 2023; Lemjabbar-Alaoui et al., 2015).

2.2 Chemotherapy for Lung Cancer

Despite the transformative impact of molecular targeted therapy and immuno-oncology in lung cancer treatment, chemotherapy remains a cornerstone of treatment for various stages and types of lung cancer, including NSCL and SCLC (Hirsch et al., 2017). The current progress in chemotherapy for lung cancer has seen significant advancements in recent years. Robust evidence supports its clinical advantages, alone or in combination, for both early and advanced lung cancer, significantly prolonging survival and enhancing quality of life. Previously, metastatic lung cancer had dire median survival, but platinum-based and newer agents ushered in substantial improvements. Adjuvant chemotherapy showed enhanced survival in early-stage resected cases, especially with cisplatin-based regimens. Novel chemotherapeutic agents and combination therapies have led to improved response rates and prolonged survival for

some patients (Grant, Hagopian, & Nagasaka, 2023). However, challenges persist, including drug resistance and varying patient responses, especially for the side effects.

Chemotherapy employs chemically synthesized drugs to target and impede the growth of tumor cells. These drugs disrupt processes like DNA and mRNA synthesis and cell division, effectively eradicating cancerous and inevitably bringing damage to normal cells. Common chemotherapy drugs include etoposide, gemcitabine, paclitaxel, and cisplatin. Frequently used chemotherapy agents encompass a range of drugs, with notable examples being etoposide, gemcitabine, paclitaxel, and cisplatin. These compounds are pivotal components of cancer treatment regimens, playing a significant role in targeting and impeding the growth of malignant cells. Etoposide, for instance, operates by inhibiting DNA replication, gemcitabine disrupts DNA synthesis, paclitaxel exerts its impact by hindering microtubule formation, and cisplatin forms cross-links in DNA strands, collectively contributing to their antitumor effects. The utilization of these chemotherapy drugs reflects their integral position in modern oncology, where their distinct mechanisms of action are strategically employed to combat various forms of cancer (Pinedo & Giaccone, 1997).

Different chemotherapy drugs have distinct toxicity profiles, which influence treatment choices, patient tolerance, and success rates. Etoposide can lead to lowered blood cell counts, increasing the risk of infections and bleeding, while gemcitabine may cause fatigue, nausea, and flu-like symptoms. Paclitaxel can induce neuropathy, characterized by tingling and numbness in extremities, and cisplatin is known for its potential to cause kidney damage and hearing loss. Neurotoxicity of chemotherapy has been linked to cognitive changes, often referred to as "chemobrain" or "chemotherapy-induced cognitive impairment." This manifests as memory, learning, concentration, and reasoning impairment during and after chemotherapy, affecting patients' quality of life. While some cases exhibit subtle, short-term effects, certain chemotherapeutic agents may cause sustained, long-term cognitive side effects, underscoring the need for balanced treatment approaches (Altun & Sonkaya, 2018). The array of side effects underscores the importance of personalized patient care, where a thorough understanding of the toxicity profiles of these drugs guides treatment decisions and proactive management strategies.

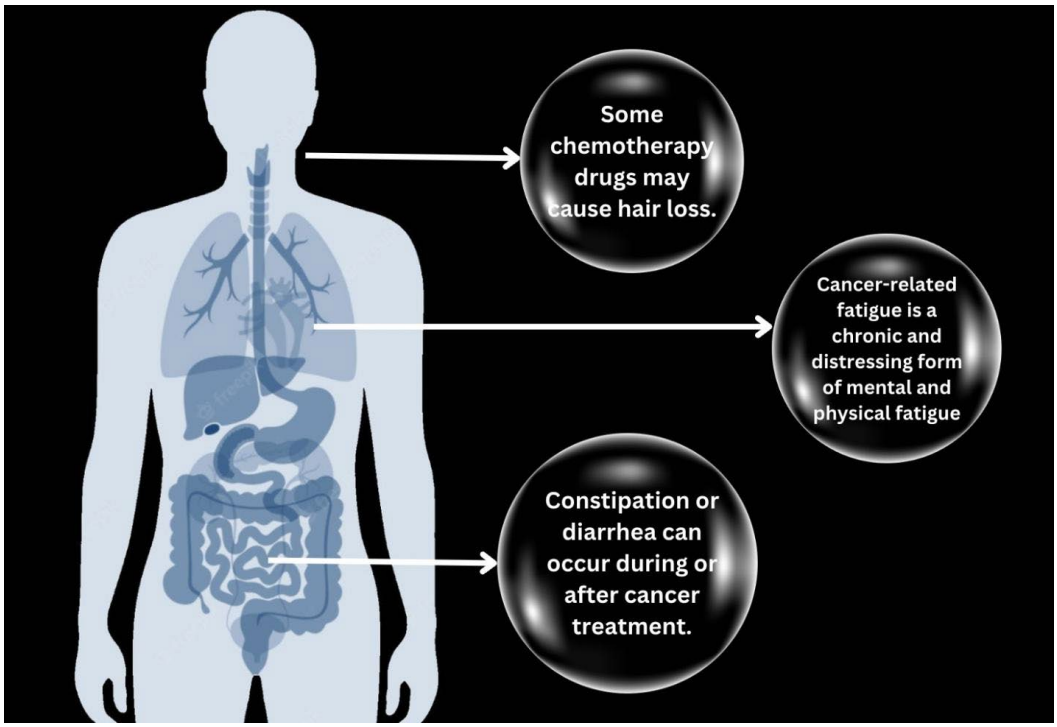

Figure 1. Side effects of lung cancer chemotherapy

3. Interventions in the Side Effects of Lung Cancer Chemotherapy

3.1 Natural Molecules

Efforts to alleviate the side effects of lung cancer chemotherapy have led to the exploration of diverse strategies. One avenue of research delves into the potential benefits of utilizing small molecules, such as plant extracts and adaptogens, which are recognized for their capacity to enhance adaptability and cognitive functions in individuals undergoing chemotherapy. A variety of natural molecules have been investigated for their potential to mitigate the adverse effects of chemotherapy. For example, curcumin, a compound found in turmeric, is known for its antioxidant and anti-inflammatory properties, and ginger has been explored as a means to reduce nausea and vomiting associated with chemotherapy (Liu et al., 2018). Green tea extract, which is rich in antioxidants, aims to provide protection to healthy cells against the damaging effects of chemotherapy (Cao, Han, Xiao, Qiao, & Han, 2016). Omega-3 fatty acids derived from sources like fatty fish and flaxseed have shown potential in countering inflammation and fatigue experienced by patients undergoing chemotherapy (Freitas & Campos, 2019). Vitamin D has been recognized for its role in promoting bone health, an aspect that can be particularly compromised during chemotherapy (Kennel & Drake, 2013). Moreover, glutamine has shown promise in reducing gastrointestinal toxicity, and acupuncture is being explored as a potential approach for managing various chemotherapy-related symptoms (Gaurav, Goel, Shukla, & Pandey, 2012). Honey, with its antioxidant and anti-inflammatory qualities, offers a unique avenue for potential protective benefits (Ahmed et al., 2018). While these natural interventions hold promise, their effectiveness and safety necessitate further rigorous investigation.

3.2 Diet Intervention

Cancer is increasingly recognized as a metabolic disorder due to distinct metabolic behaviors in tumor cells compared to healthy cells. Tumor cells not only exhibit unique metabolic patterns but also induce systemic metabolic alterations (Amoedo, Valencia, Rodrigues, Galina, & Rumjanek, 2013). Utilizing dietary approaches to target metabolism is gaining prominence in cancer treatment. Interventions targeting systemic metabolism hold the potential to enhance therapeutic effectiveness and patients' treatment response.

3.2.1 Caloric Restriction

Caloric restriction (CR), renowned for enhancing health span and lifespan, is under scrutiny as a potent intervention across models. However, its mechanisms curbing tumorigenesis and affecting chemotherapy's impact on tumors remain not fully understood. Metabolic dysregulation and glycolysis inhibition likely govern cancer cell growth control and drug resistance. Immunosuppressants, such as sirolimus, are considered CR mimetics, boosting insulin sensitivity, oxygen use, and lipid profiles. Certain immunosuppressants, e.g., 2DG and resveratrol, safeguard normal cells from stress-induced mortality. CR-triggered ketone elevation might protect normal cells via ROS reduction. A desirable CR mimetic should lower blood glucose, insulin, and IGF-1, and elevate ketone bodies. Prolonged CR is cautioned against for cancer patients due to cachexia risks and potential chemotherapy dose reduction. Mimetic diets and augmented platinum-based pemetrexed chemotherapy display potential efficacy for advanced disease. Restrictive diets impact cancer cell bioenergetics and metabolic pathways, lowering vital metabolites like glucose and amino acids (Brandhorst & Longo, 2016).

SIRT5 and SIRT1 proteins link CR to cancer benefits, potentially via inhibiting the Warburg effect (Bringman-Rodenbarger, Guo, Lyssiotis, & Lombard, 2018; Lin & Fang, 2013). Pharmaceutical focus on CR mimetics aims to replicate its advantages without major food reduction. Sirolimus and related compounds show potential, enhancing insulin sensitivity and lipid profiles. CR mimetics combined with traditional anticancer drugs may reduce toxicity and

improve effectiveness (O'Flanagan, Smith, McDonell, & Hursting, 2017). Integrating CR with immunogenic cell death induction seeks robust anticancer immune responses. Metabolism's role in immune cell activity suggests CR's relevance.

3.2.2 Fasting-Mimicking Diets

Fasting-mimicking diets (FMD), comprising plant-based low-calorie, carbohydrate- and protein-restricted regimens, synergize with cytotoxic drugs in preclinical human cancer models, curbing cancer while safeguarding normal cells. FMD's anticancer effects stem from reduced blood glucose, insulin, and IGF-1. Preclinical data hint FMD boosts antitumor immunity by altering lymphocyte infiltration. Periodic FMD, more palatable than fasting, doesn't compromise lean body mass (Brandhorst, 2021). Fasting mimicking diet (FMD) exploits metformin's potential in LKB1-inactive lung adenocarcinoma, enhancing effects through nutrient deprivation. Clinical trials, like the FAME trial, explore combining metformin and FMD with chemotherapy to enhance progression-free survival (Brandhorst, 2021).

3.2.3 The Mediterranean Diet

The Mediterranean diet, characterized by its emphasis on whole foods, healthy fats, and plant-based ingredients, is thought to offer potential benefits for individuals undergoing chemotherapy and dealing with its associated side effects. While research continues, this dietary pattern shows promise in providing nutrient-rich foods that can support the immune system and overall health during chemotherapy. The diet's anti-inflammatory properties, thanks to components like olive oil, nuts, and colorful fruits and vegetables, may help manage inflammation often associated with both cancer and chemotherapy side effects. Additionally, its focus on gut health, potential nausea relief from ingredients like ginger, and the inclusion of heart-healthy fats could contribute to mitigating side effects and maintaining overall well-being. Consultation with a healthcare professional or registered dietitian is essential to tailor the Mediterranean diet to individual needs and treatment regimens (Mentella, Scaldaferri, Ricci, Gasbarrini, & Miggiano, 2019).

3.3 Gut Microbiota

Enhancing chemotherapy efficiency and mitigating side effects through the regulation of gut microbiota is an emerging area of research. One strategy involves incorporating prebiotics and probiotics into the diet. Prebiotics, found in foods like garlic, onions, and bananas, promote the growth of beneficial gut bacteria, while probiotics, present in yogurt and fermented foods, introduce live microorganisms that can improve gut microbial balance during chemotherapy. Including dietary fiber from whole grains, fruits, and vegetables can positively influence the gut microbiota composition as fiber serves as a food source for beneficial bacteria, helping them thrive and maintain a diverse microbiome (Ma et al., 2019).

Polyphenol-rich foods such as berries, green tea, and dark chocolate may also have a positive impact on the gut microbiota and reduce inflammation caused by chemotherapy. These polyphenols possess antioxidant and anti-inflammatory properties that can benefit gut health. However, it is crucial to avoid unnecessary antibiotic use as overuse can disrupt the gut microbiota. Preserving the diversity and balance of gut bacteria is essential for overall gut health during chemotherapy (Kumar Singh et al., 2019). Additionally, fecal microbiota transplant (FMT), a novel procedure involving the transfer of fecal matter from a healthy donor to a patient's gut, is being explored for its potential to restore a balanced microbiota and improve gut health during chemotherapy. However, FMT is still in the experimental stage, and its long-term safety and efficacy require further investigation (Chen, Wu, Jin, Wang, & Cao, 2019).

Overall, staying hydrated and well-nourished during chemotherapy is vital for maintaining a healthy gut lining and supporting the growth of beneficial bacteria. It is recommended to avoid excessive consumption of added

sugars and processed foods, as diets high in these elements can negatively affect gut microbiota composition. Opting for whole, unprocessed foods can contribute to better gut health (Zhang et al., 2015).

3.4 Adjuvant Therapy and Combined Therapy

Combined therapy for lung cancer involves the use of multiple treatment modalities in a coordinated approach to achieve enhanced therapeutic outcomes. This approach aims to target cancer cells from different angles, potentially increasing effectiveness while minimizing resistance. Combined therapy for lung cancer patients offers numerous advantages by employing multiple treatment modalities in a coordinated approach. The benefits include increased treatment efficacy as different approaches target cancer cells from various angles, potential synergistic effects that enhance treatment outcomes, and the ability to overcome resistance that cancer cells may develop against single treatments. Additionally, combining therapies can lead to reduced side effects by allowing lower individual treatment doses while maintaining effectiveness. Improved survival rates, personalized treatment options, prevention of recurrence, and better disease control contribute to enhanced quality of life for patients. The approach also maximizes therapeutic options, especially in addressing the complexities of lung cancer subtypes and mutations (Wu, Leng, Cun, Foged, & Yang, 2017).

Adjuvant therapy for lung cancer is a treatment approach that involves administering additional therapy after the primary treatment. Adjuvant therapies play a pivotal role in enhancing the outcomes of chemotherapy for lung cancer by mitigating side effects and improving treatment efficacy. Among the various adjuvant strategies, one promising avenue is the utilization of natural molecules and dietary interventions as we discussed above. Compounds such as Quercetin have exhibited potential as adjuvants to chemotherapy, enhancing its effectiveness while simultaneously reducing toxic side effects on normal tissues. Targeted therapies can be integrated as adjuvants to chemotherapy, specifically tailored to the genetic profile of the tumor. This personalized approach holds promise for reducing off-target effects and enhancing treatment selectivity. Immunotherapy, with its ability to harness the immune system to target cancer cells, may also serve as an adjuvant therapy to chemotherapy, potentially boosting the immune response and extending treatment benefits (Sangha, Price, & Butts, 2010).

In conclusion, the landscape of adjuvant therapies for lung cancer chemotherapy is dynamic and multifaceted. The integration of natural molecules, dietary interventions, targeted therapies, immunotherapy, and microbiota modulation as adjuvant strategies could collectively contribute to improving the side effect profile of chemotherapy. As research advances, the potential to harness these adjuvant therapies to optimize lung cancer treatment outcomes and enhance patient well-being becomes increasingly promising.

4. Conclusions and Perspectives

The multifaceted nature of lung cancer demands a comprehensive approach to treatment, and this discussion section seeks to synthesize and reflect upon the diverse themes explored throughout this paper. The central role of chemotherapy in lung cancer management has been established, providing a foundation for therapeutic intervention. However, the concomitant side effects associated with chemotherapy pose significant challenges to patient well-being. The investigation into measures aimed at alleviating chemotherapy side effects is a pressing and essential endeavor to enhance the overall chemotherapy process.

Dietary interventions, particularly the Caloric restriction, fasting mimicking diet and Mediterranean diet, emerge as promising strategies to address chemotherapy-induced side effects and improve patient outcomes. The potential synergy between the effects brought by diets and chemotherapy underscores the importance of holistic patient care. The exploration of combined therapies and adjuvant therapies further reinforce this principle, demonstrating the potential for improved treatment efficacy and the mitigation of drug resistance. The integration of targeted therapy,

immunotherapy, and dietary strategies with chemotherapy holds promise for achieving comprehensive responses and enhancing patient quality of life.

The interplay between gut microbiota and chemotherapy outcomes introduces a novel dimension to lung cancer treatment. Modulating the gut microbiome presents a tantalizing avenue to influence treatment responses and potentially reduce toxicity. As research in this area matures, the prospect of tailored interventions that optimize chemotherapy efficacy gains prominence.

In essence, this paper presents a comprehensive landscape of lung cancer treatment, weaving together diverse threads that collectively contribute to the improvement of chemotherapy. The integration of conventional therapies with innovative strategies, informed by the potential of natural molecules, dietary interventions, and gut microbiota modulation, underscores the necessity for a holistic paradigm shift in lung cancer care. As the field continues to evolve, translating these insights into meaningful clinical applications holds the promise of transforming the outlook for lung cancer patients, optimizing treatment responses, and ultimately enhancing their quality of life.

Reference

Ahmed, S., Sulaiman, S. A., Baig, A. A., Ibrahim, M., Liaqat, S., Fatima, S., . . . Othman, N. H. (2018). Honey as a Potential Natural Antioxidant Medicine: An Insight into Its Molecular Mechanisms of Action. *Oxid Med Cell Longev, 2018*, 8367846. doi:10.1155/2018/8367846

Altun, I., & Sonkaya, A. (2018). The Most Common Side Effects Experienced by Patients Were Receiving First Cycle of Chemotherapy. *Iran J Public Health, 47*(8), 1218-1219. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/30186799

Amoedo, N. D., Valencia, J. P., Rodrigues, M. F., Galina, A., & Rumjanek, F. D. (2013). How does the metabolism of tumour cells differ from that of normal cells. *Biosci Rep, 33*(6). doi:10.1042/BSR20130066

Birring, S. S., & Peake, M. D. (2005). Symptoms and the early diagnosis of lung cancer. *Thorax, 60*(4), 268-269. doi:10.1136/thx.2004.032698

Brandhorst, S. (2021). Fasting and fasting-mimicking diets for chemotherapy augmentation. *Geroscience, 43*(3), 1201-1216. doi:10.1007/s11357-020-00317-7

Brandhorst, S., & Longo, V. D. (2016). Fasting and Caloric Restriction in Cancer Prevention and Treatment. *Recent Results Cancer Res, 207*, 241-266. doi:10.1007/978-3-319-42118-6_12

Bringman-Rodenbarger, L. R., Guo, A. H., Lyssiotis, C. A., & Lombard, D. B. (2018). Emerging Roles for SIRT5 in Metabolism and Cancer. *Antioxid Redox Signal, 28*(8), 677-690. doi:10.1089/ars.2017.7264

Cao, J., Han, J., Xiao, H., Qiao, J., & Han, M. (2016). Effect of Tea Polyphenol Compounds on Anticancer Drugs in Terms of Anti-Tumor Activity, Toxicology, and Pharmacokinetics. *Nutrients, 8*(12). doi:10.3390/nu8120762

Chen, D., Wu, J., Jin, D., Wang, B., & Cao, H. (2019). Fecal microbiota transplantation in cancer management: Current status and perspectives. *Int J Cancer, 145*(8), 2021-2031. doi:10.1002/ijc.32003

Cooper, W. A., Lam, D. C., O'Toole, S. A., & Minna, J. D. (2013). Molecular biology of lung cancer. *J Thorac Dis, 5 Suppl 5*(Suppl 5), S479-490. doi:10.3978/j.issn.2072-1439.2013.08.03

Freitas, R. D. S., & Campos, M. M. (2019). Protective Effects of Omega-3 Fatty Acids in Cancer-Related Complications. *Nutrients, 11*(5). doi:10.3390/nu11050945

Gaurav, K., Goel, R. K., Shukla, M., & Pandey, M. (2012). Glutamine: A novel approach to chemotherapy-induced toxicity. *Indian J Med Paediatr Oncol, 33*(1), 13-20. doi:10.4103/0971-5851.96962

Giaccone, G., & He, Y. (2023). Current knowledge of small cell lung cancer transformation from non-small cell lung cancer. *Semin Cancer Biol, 94*, 1-10. doi:10.1016/j.semcancer.2023.05.006

Grant, C., Hagopian, G., & Nagasaka, M. (2023). Neoadjuvant Therapy in Non-Small Cell Lung Cancer. *Crit Rev Oncol Hematol*, 104080. doi:10.1016/j.critrevonc.2023.104080

Henry, D. H., Viswanathan, H. N., Elkin, E. P., Traina, S., Wade, S., & Cella, D. (2008). Symptoms and treatment burden associated with cancer treatment: results from a cross-sectional national survey in the U.S. *Support Care Cancer, 16*(7), 791-801. doi:10.1007/s00520-007-0380-2

Hirsch, F. R., Scagliotti, G. V., Mulshine, J. L., Kwon, R., Curran, W. J., Jr., Wu, Y. L., & Paz-Ares, L. (2017). Lung cancer: current therapies and new targeted treatments. *Lancet, 389*(10066), 299-311. doi:10.1016/S0140-6736(16)30958-8

Inamura, K. (2017). Lung Cancer: Understanding Its Molecular Pathology and the 2015 WHO Classification. *Front Oncol, 7*, 193. doi:10.3389/fonc.2017.00193

Kennel, K. A., & Drake, M. T. (2013). Vitamin D in the cancer patient. *Curr Opin Support Palliat Care, 7*(3), 272-277. doi:10.1097/SPC.0b013e3283640f74

Kumar Singh, A., Cabral, C., Kumar, R., Ganguly, R., Kumar Rana, H., Gupta, A., . . . Pandey, A. K. (2019). Beneficial Effects of Dietary Polyphenols on Gut Microbiota and Strategies to Improve Delivery Efficiency. *Nutrients, 11*(9). doi:10.3390/nu11092216

Lemjabbar-Alaoui, H., Hassan, O. U., Yang, Y. W., & Buchanan, P. (2015). Lung cancer: Biology and treatment options. *Biochim Biophys Acta, 1856*(2), 189-210. doi:10.1016/j.bbcan.2015.08.002

Lin, Z., & Fang, D. (2013). The Roles of SIRT1 in Cancer. *Genes Cancer, 4*(3-4), 97-104. doi:10.1177/1947601912475079

Liu, Z., Huang, P., Law, S., Tian, H., Leung, W., & Xu, C. (2018). Preventive Effect of Curcumin Against Chemotherapy-Induced Side-Effects. *Front Pharmacol, 9*, 1374. doi:10.3389/fphar.2018.01374

Ma, W., Mao, Q., Xia, W., Dong, G., Yu, C., & Jiang, F. (2019). Gut Microbiota Shapes the Efficiency of Cancer Therapy. *Front Microbiol, 10*, 1050. doi:10.3389/fmicb.2019.01050

Mentella, M. C., Scaldaferri, F., Ricci, C., Gasbarrini, A., & Miggiano, G. A. D. (2019). Cancer and Mediterranean Diet: A Review. *Nutrients, 11*(9). doi:10.3390/nu11092059

Nooreldeen, R., & Bach, H. (2021). Current and Future Development in Lung Cancer Diagnosis. *Int J Mol Sci, 22*(16). doi:10.3390/ijms22168661

O'Flanagan, C. H., Smith, L. A., McDonell, S. B., & Hursting, S. D. (2017). When less may be more: calorie restriction and response to cancer therapy. *BMC Med, 15*(1), 106. doi:10.1186/s12916-017-0873-x

Pinedo, H. M., & Giaccone, G. (1997). Chemotherapy. *Lancet, 349 Suppl 2*, SII7-9. doi:10.1016/s0140-6736(97)90012-x

Sangha, R., Price, J., & Butts, C. A. (2010). Adjuvant therapy in non-small cell lung cancer: current and future directions. *Oncologist, 15*(8), 862-872. doi:10.1634/theoncologist.2009-0186

Thandra, K. C., Barsouk, A., Saginala, K., Aluru, J. S., & Barsouk, A. (2021). Epidemiology of lung cancer. *Contemp Oncol (Pozn), 25*(1), 45-52. doi:10.5114/wo.2021.103829

Wu, L., Leng, D., Cun, D., Foged, C., & Yang, M. (2017). Advances in combination therapy of lung cancer: Rationales, delivery technologies and dosage regimens. *J Control Release, 260*, 78-91. doi:10.1016/j.jconrel.2017.05.023

Zhang, Y. J., Li, S., Gan, R. Y., Zhou, T., Xu, D. P., & Li, H. B. (2015). Impacts of gut bacteria on human health and diseases. *Int J Mol Sci, 16*(4), 7493-7519. doi:10.3390/ijms16047493