Environmental factors on cancer metastasis

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Abstract

Nearly 40% of American men and women will receive a cancer diagnosis in their lifetime. Causes of such originate from aspects of one's genetics, lifestyle, and simple random mutation. Any one of these factors can elicit some sort of out-of-control cell proliferation, otherwise known as cancer. Most interestingly, however, is the environmental or lifestyle influences on one's likelihood of developing cancer -- and, more importantly, cancer metastasis itself. Metastasis is the process of carcinogenic cells traveling throughout the body to infect and spread to different areas of it. As an example, when breast cancer metastasizes, it typically spreads to the skeletal system. Metastasis is a critical process in the progression of cancer's stages; cancers are classified as stage IV once they begin to metastasize. As such, it is important to consider and realize the external effects of one's lifestyle on the speed and scope of the process. Three factors have shown to be especially notable in terms of their effect on carcinogenic aggression and spread: the chemical changes as a result of chronic stress, chemical shifts due to one's lifestyle/habits, and exposure to carcinogenic chemicals – i.e. pollution.

Stress and metastasis

Stress is a part of life for virtually every human on Earth. Everyday things like relationships, worrying about the future, and work/schooling -- along with significant events like losing a job or getting diagnosed with a serious disease -- cause varying levels of stress on a large majority of the population. It is known that stress can cause adverse health issues, like hypertension or mental health problems. Chronic stress over many years can have life-threatening effects -- like an increased risk of heart failure -- and, according to recent research, can even aid cancer to metastasize.

Resulting from stress, the human immune system undergoes changes -- temporary or otherwise. In early life, exposure to stressors such as abuse or poverty can cause changes in the body. Primarily, immune system dysregulation. It was found that immune cells in children with greater exposure to stressors during early life produced a greater concentration of pro-inflammatory molecules. A positive correlation was thus established between early lifetime stressors and inflammatory markers in the body, indicative of the effect of stress on the immune system (Morey, et al., 2015, p. 5).

Effectively, exposure to chronic stress hurts the regulative abilities of the immune system. This, as a result, can negatively affect the body's ability to regulate cancerous cells; a weaker immune system will generally be less able to regulate the proliferation of cancerous cells. Additionally, as people age, the impairments of chronic stress will be magnified to a greater extent. From an immunological perspective, chronological aging works in tandem with long-term stress to accelerate the aging and decline of the immune system. It has been found that a negative correlation is established between age and the ability to cease cortisol production in response to stress: as people get older, their bodies start to function less and less effectively. With it, too, long-term accumulation of stress-induced cortisol within the body can lead to an immune system with a far-too high concentration of stress hormones, which subsequently increases production of inflammatory signaling matter as well (Morey et al., 2015, p. 6). With biological immunity itself, stress is also a factor in health. Within the immune system, cells like lymphocytes normally mobilize in preparation of fighting infection. However, evidence suggests that immune cells take priority in signaling, rather than defensive action, during times of stress. Since immune responses are energetically costly, this weakens the immune system over time (Morey et al., 2015, p. 8). The shift to signaling rather than response inhibits the immunological response to pathogenic invaders. As such, the body is impaired while in times of stress-induced immunological inhibition, and causes a weaker response when unstressed. A less-effective response to cancer is established as a result. Overall, stress negatively affects the immune system and thus can establish pro-metastasis microenvironments as a result.

More specifically, though, is the body's reaction involving particular molecules called glucocorticoids that are released during times of stress. These hormones cause changes within immune cells -- neutrophils -- and increase the risk of cancer metastasizing. These neutrophils release their own structures called neutrophil extracellular traps (NETs) which themselves contribute to a microenvironment more suited for cancer to spread. Evidence has established a correlation between NET concentration and risk of cancer spreading -- even as much as double the normal chances (He, et al., 2024, p. 1). This ultimately ties back to stress, as chronic exposure to stress increases glucocorticoid production, which induces neutrophils to release more NETs, which then increases the risk of metastasis.

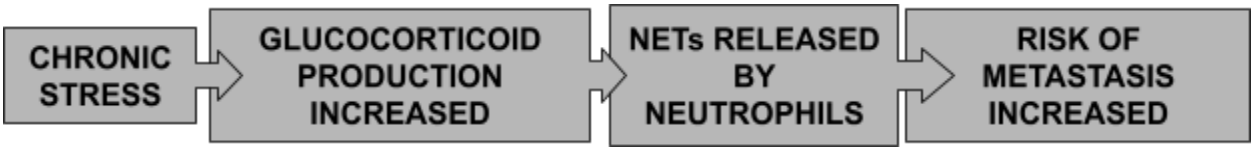

Figure I: chronic stress has the potential to initiate a process which would exacerbate cancerous metastasis due to greater concentration of intracellular fibrous material -- NETs, in this case -- which allows cancerous cells to spread more rapidly.

A study concerning mice with breast cancer was conducted to strengthen the link between stress exposure and the risk of metastasis. In one group of subjects, the mice were exposed to constant, low-level stress. Another group was studied while experiencing random, intermittent, more-intense tension. It was found that both groups experienced larger mammary tumors and higher rates of lung metastases than that of a group of mice with no exposure to stress (Reynolds, 2024, p.12 - 15). It was clear that any amount of chronic stress has some impact on the progenesis of cancer throughout the body. Despite these findings, however, it was soon discovered that the effects of stress were not directly influencing the rates of metastasis, but instead the microenvironments which the cancers existed in. As such, new research was then initiated to examine the extent of stress' impact on visceral microenvironments. Researchers turned their attention to the parts of the body impacted by metastasis -- in the mice's case, lung tissue -- and discovered neutrophil cells that were impacted by glucocorticoids. The latter induced the former into migrating to lung tissue, which they, in turn, stimulated different cells into producing fibronectin within the lungs. The result of this process favors a microenvironment different from that of the original mammary tumor, which increases the risk of metastasis. Alongside fibronectin, NETs has been known to promote metastasis by aiding cancerous cells in forming tumors in different parts of the body (Reynolds, 2024, p. 18-12; NCI, 2016, p. 3). As the glucocorticoid concentration within the body is increased due to stress, more and more neutrophils are being stimulated to release NETs. Thus, since NETs have demonstrated a strong correlation with promoting metastasis, stress begins a process which ultimately contributes to a metastatically-favorable environment.

Lifestyle and metastasis

It has been pre-established that lifestyle choices like inactivity, smoking/drinking, and obesity can cause general unhealthiness, however the more important recurrences stemming from these behaviors is the prevalence of metastasis among cancer patients. Cancer metastasis is an increasingly-common occurrence that affects 20% of colorectal

cancer patients and nearly 30% of breast cancer patients (An et al., 2024, p. 1; NBCF, 2024, p. 5). As such, it is important to recognize the lifestyle effects of cancer patients as a whole to mitigate its spread.

Approximately 16% of adults worldwide are classified as obese (WHO, 2024, p. 8). This epidemic is on the rise as nations develop, with high-calorie food becoming increasingly convenient, an increasing dependency on automotive travel, and socioeconomic factors limiting what diets can be maintained. At the same time, global cancer cases are continually rising as well. This in itself is the result of a myriad of different factors, however, it has been discovered that the heightened obesity rates play a part in the presence and severity of cancer worldwide.

It is known that fat cells provide a suitable environment for cancer to develop and spread into. It's part of the reason why breast cancer is the single most common form in the United States, accounting for 16% of American cancer cases and 7% of cancer deaths (NCI, 2024, fig. 1). Since human breast tissue is mainly composed of fat deposits, it is clear that adipose tissue affects the development of cancer in a significant way. Specifically, it aids in the survivability of tumors, which enables its spread across long distances within the body (Annett, Moore, Robson, 2020, p. 1). As a result, the prognosis for patients suffering with obesity is worse than that of a patient with a healthier weight, as metastasis is accelerated with an increased amount of tumor-friendly tissue. Additionally, a percentage of patients with obesity also neglect regular physical activity. A 2021 study of different demographics of German adults concluded that the rate of physical inactivity was higher among those identifying as obese. As much as 56% of the studied adults with an obese-classified BMI reported no physical activity in a week (Linder, et al., 2021, fig. 1). This is important to consider because physical activity is linked to suppressing metastasis in itself. It has been discovered that exercise changes the immune system to regulate metastasis by mobilizing cells equipped to kill tumors to metastatic locations. This helps mitigate the metastatic processes known as invasion (where cancer cells translocate to a different part of the body) and colonization (where an entire tumor is formed in a new location) (Zheng et al., 2022, p. 5 & 29). The correlation between obesity and physical inactivity, the rising prevalence of obesity, and the effects of physical inactivity on metastasis create a dangerous feedback loop which promotes carcinogenic development and prognostication. These factors have a profound effect on physical health and management of cancer, since the body is worse-equipped to survive because of a person's lifestyle decisions or circumstances.

Additionally, the development of cancer is closely linked to harmful substance usage and dietary choices. For example, an astounding 71% of lung cancer deaths are attributed to tobacco usage. Lung cancer is the most deadly form of cancer in the world. It is estimated that more than 125,000 American adults will die from the disease. The second most deadly form is colorectal cancer, with only ~50,000 estimated deaths. Lung cancer is almost three times more deadly than the second leading cause of cancer death. So, the danger of smoking as it relates to cancer is clearly evident (Wiederpass, 2010, p. 1; NCI, 2024, fig. 1). In patients with colorectal cancer, it was found that adverse dietary intake can also impact metastasis. A 2024 review has identified excessive red and processed meat as a risk factor in metastatic colorectal cancer. Specifically, poor dieting resulted in an ~17% chance increase of metastasis for every 100 grams of red meat eaten daily; for every 50 grams of processed meat, the risk increased by ~18%. What's more, around 80% of stage III & metastatic patients in the referenced experiment did not meet the FDA-required amount of fruit, vegetables, or dairy products (An et al., 2024, p. 33). Despite low-moderate alcohol consumption posing no significant effect on metastatic colorectal cancer, binge drinking is especially dangerous on carcinogenesis and carcino-prognosis. People who drink more than 4 times a day have a 52% chance of developing colorectal cancer. Additionally, among subjects in a Canadian study from 2012, those who consumed alcohol at least once per week for six months or more, and had a BMI greater than 30, had a significant increase in colorectal cancer risk (An et al., 2024, 35). Ultimately, the habits and behavior that people engage in daily have significant negative impacts on health. These impacts are then magnified in those suffering from cancer, and as such it is pertinent to recognize potentially harmful life choices.

Exposure and metastasis

In the post-Industrial Revolution world, technological innovations have changed the world in which everyday people live -- for better or worse. In terms of the downsides, air and water pollution have characterized the environmental landscape for decades. As a byproduct of the pollutants found in a majority of the aspects of life, humanity is constantly being exposed to a myriad of foreign (potentially harmful) substances. Some of these substances have the potential to cause cancer or accelerate its spread. It is vital, then, to be able to recognize how these substances can affect the development of cancer to take steps to mitigate it.

At an increasing rate, the specific chemical environment of a breast cancer patient is becoming increasingly more involved in the development of metastasis.

Things like pollution, or other harmful chemicals, can significantly disrupt the endocrine signaling pathways associated with preventing metastasis. Also, these disruptions increase the body's resistance to chemotherapy during treatment (Koual, et al., 2020, p. 1). As it was discovered, breast cancer patients with TCDD in their adipose tissue -- which is a potent pollutant and carcinogen -- were associated with lymph node metastasis. The compound achieves this by acting upon the environmental *aryl hydrocarbon receptor* (AhR), which is involved in gene expression. The direct correlation between the AhR pathway and metastasis is unclear, but still presents some influence on the latter. It also has been shown to initiate epithelial-mesenchymal transition (EMT), which is a form of metastasis involving cancerous stem cells (CSCs), and reduce mitochondrial function. Thankfully, industrial processes which release TCDD (particularly certain manufacturing techniques) have been banned since the 1970s. Although it has been discovered as a facilitator to some cancer progressions, TCDD can actually aid in tumor suppression in certain cases. For example, it can disrupt certain gene encoders and act as a tumor suppressant, using the same signaling pathway (AhR) that was involved in genomic expression. Another class of dangerous chemicals involved in metastasis is *polychlorinated biphenyls*, or PCBs. These were originally used in industrial settings, however were banned internationally due to health concerns. Despite these compounds being banned since the 1980s, people could still potentially be exposed to them in their diet, in the atmosphere, at the workplace, or in consumer products. PCBs pose a significant threat because of their environmental persistence; they take many millennia to degrade and exit the human biosphere. Like TCDD, PCBs will aid in lymph node metastasis. Additionally, PCBs in the body have been shown to increase migration rates of certain cells & tumors, as well as activate specific enzymes which accelerate lung, bone, and liver metastasis. Toxic metals like iron, copper, zinc, lead, chromium, or nickel have also been shown to have correlation with poor breast cancer prognostics. These metals, similar to other toxic materials discussed, will interact with genomic expression and allow tumors to spread with far less resistance (Koual, et al., 2020, p. 7, 8, 23).

Although a subject of much controversy, these disruptions stemming from environmental chemicals will aid tumorous material into developing chemoresistance to treatment. It has been concluded that the two major processes which aid chemoresistance are the epithelial-mesenchymal transition and cancer stem cell development. It was hypothesized that EMT cells have greater replicative properties than that of non-EMT cells, which would allow these cells to be more resistant to drugs that were already tailored to the latter. As for CSC development, the principle is the

same. CSCs have the same properties as regular stem cells, so they are able to more-rapidly replicate and resist treatment (Koual et al., 2020, 41).

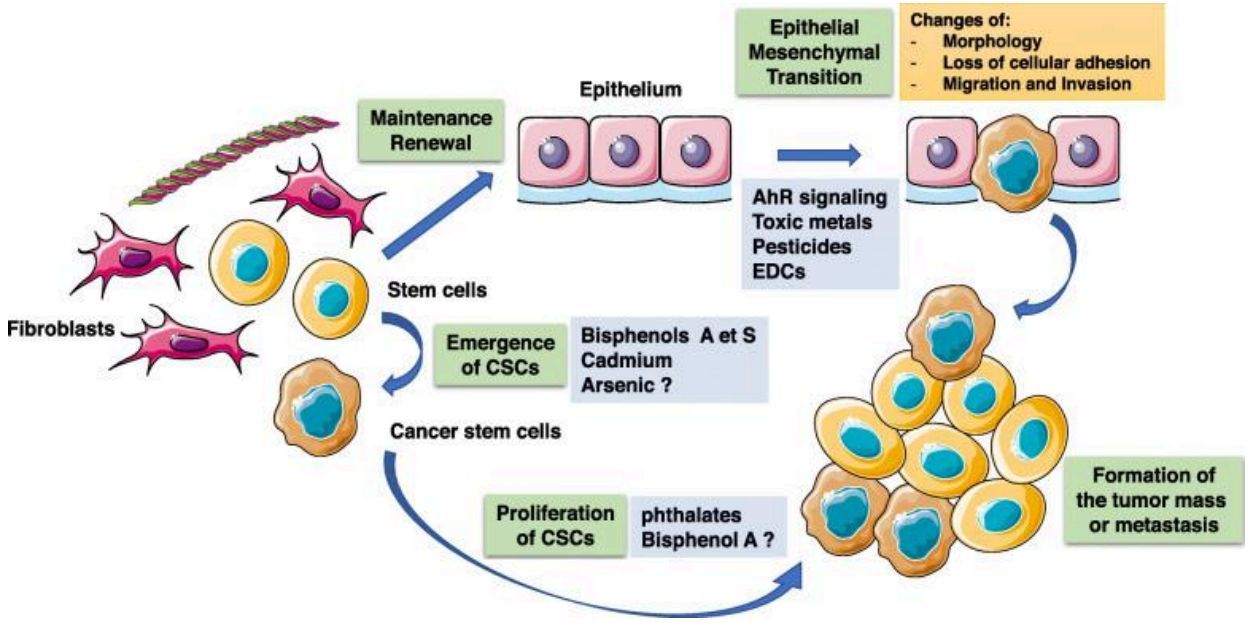

Figure II: Epithelial-to-mesenchymal transition and appearance of cancer stem cells are two mechanisms which are suspected to lead to the occurrence of metastasis. EMT is associated to the phenotypical acquisition of cellular properties which leads to the migration and invasion of primary tumor cells while cancer stem cells conserve cellular properties of stem cells (important for maintenance and renewal of the breast cellular epithelium) which maintain cancer proliferation, metastatic dissemination and resistance to anticancer treatment. The figure also synthesized the processes which are targeted by environmental pollutants (orange squares) (Koual, et al., 2020, fig. 2 & caption).

What to do

As cancer rates rise at unprecedented levels and carcinogens become an increasingly-present part of life, it is important to recognize potential accelerants and take action against them. The single most impactful thing anyone can do to help mitigate metastasis (and cancer as a whole) is living a healthy and active lifestyle. Strengthening the body - including laying off excessive alcohol, smoking, and unhealthy foods - will ultimately reduce the risk of cancer occurrence and its effects. Also, certain aspects of cancer progenesis are unavoidable, whether it be inhaling polluted air or simple random chance. This only makes preventative action more crucial; if someone has any chance of cancer in living a normal life, why exacerbate it by engaging in unhealthy habits?

Cancer is a uniquely-alarming worldwide health concern. It forms, spreads, and kills like no other disease on Earth. The relevance of cancer awareness and prevention, then, is becoming a much-needed part of common knowledge. Every part of human daily living -- diet, personal choices, even just living itself -- can and does contribute to its development. More and more people are dying every day, which can be attributed to some extent to ignorance on how to prevent or relieve cancer and its effects. Knowledgeability on this topic, at this point, is a matter of preventing death itself rather than simply for knowledge's sake.

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