As of 2018 it is estimated that 1/3 of men and women will develop cancer in their lifetime [1]. There are numerous potential reasons for the growing incidence of cancer. Undeniably increased lifespan compared to our ancestors is a major factor as 87% of people diagnosed with cancer are over 50 years old [1]. However, lifestyle also plays an important role in the development and progression of cancer [11]. In recent years there has been a decline in cancer mortality due to earlier detection, better treatments and decreasing rates of smoking [1]. Despite this, increasing survival rates have led to an increased incidence of secondary cancers developing [2]. Additionally, stage IV cancer 5-year survival rates remain low. Therefore, new ideas are needed in cancer research. One promising area of research is evolutionary medicine; by looking at how evolutionary principles influence the growth and development of cancer, researchers may be able to develop new strategies for preventing and treating cancer.

Researchers have hypothesized that cancer cell development as well as the clonal proliferation of cancerous cells follows Darwinian mechanics [6-7]. Cellular stress causes mutations which in turn creates variation. Unfavorable mutations, which decrease cellular fitness, are selected against and favorable mutations, which increase cellular fitness, are selected for. Fitness is determined by a cell's phenotype not its genotype. Due to shared selection pressures, cancerous cells converge on similar phenotypic traits; these traits are known as the hallmarks of cancer [12]. Cells with increased fitness proliferate and create clones which can further undergo mutations, which in turn can further enhance their fitness. Stem cells have been hypothesized to be the unit of selection; these cells express increased plasticity, have unlimited replicative potential, and survive long enough to accrue the mutations necessary to become cancerous [17].

It has also been hypothesized that the tumor microenvironment stresses and applies selective pressure on cells [13]. The tumor microenvironment consists of all the cells, vessels, nutrients and soluble factors, such as cytokines, that are found surrounding and interacting with the tumor [16]. Additionally, cells are not passive but can interact with and engineer the environment around them [13-15]. Cells can also interact with one another, and can compete and cooperate for resources [5,18]. This leads to tumor heterogeneity as different subclones occupy different niches. Increased tumor heterogeneity is associated with more aggressive tumors and may increase the metastatic potential of a tumor [5,18].

It has been proposed that cellular stress promotes cellular heterogeneity [22]. Increased heterogeneity leads to cellular evolution, which may in the end lead to the development of cancer [22]. Therefore, anything that leads to cellular stress, such as an inflammatory microenvironment, may lead to the development of cancer. The goal of cancer prevention strategies should be to decrease overall cellular stress. However, not all stress is deleterious to our health. Intermittent exposure to stress, such as exercise, has beneficial effects [73]. This is known as eustress. When stress

begins to negatively affect our body it is known as distress. Many stressors can be both beneficial or harmful depending on the dose and duration of exposure [74-75]. One major source of stress comes from our modern lifestyles. There is discordance between how we evolved to live and how we currently live which causes a host of issues. This is known as evolutionary mismatch theory [70-71].

Cancer is not a modern disease as there is robust evidence of cancer in the archeological record [24]. However, it appears that cancer rates in the past century have steadily increased [25]. Although there are limited data on cancer rates among hunter gatherer populations, what data there are suggest their rates of cancer, as well as other chronic diseases, were significantly lower compared to modern humans [26-27]. Therefore, it is prudent to look at the lifestyles of our ancestors to gain insight into how best to avoid lifestyles that may promote the development of cancer as well as chronic illnesses.

Some mismatches are well known causes of cancer, and society has already begun shifting away from these behaviors. For example, it is well established that excess UV exposure causes skin cancer [28], smoking causes lung cancer [29], excess salted food consumption causes gastric cancer [30], and chronic infections can lead to a host of different cancers [31]. However, there are many other behaviors that have been hypothesized to be mismatches and require further research and investigation. The reason they are less well known is because they may work through multiple mechanisms and may not directly cause cancer. Instead they may increase systemic stress driving cellular mutation that may lead to cancer as discussed above. Just this year it was found that a lack of exposure to infectious stimuli in infancy can pre-dispose children to develop acute lymphoblastic leukemia [32]. However, inherited mutations, diet and chance also play a role [32].

Our modern diets may play a role in the development of cancer; however, the extent of that role is currently unknown. Depending on the type of cancer, intake of all macronutrients has been associated with the development of cancer. When comparing modern diets to those of hunter-gatherer populations, the quality of our diets is significantly worse. We consume food that contains less micronutrients, less fiber, more toxins, is more processed, and is more inflammatory [33-34]. We also consume more calories and our rates of obesity are the highest they have ever been. Increased body fat increases the risk of developing cancer [35] while also increasing inflammation [36-37] and suppressing the immune system [38]. Our diet as well as obesity also has a significant impact on our microbiome [39]. Industrialized humans have the lowest abundance and diversity of gastrointestinal microorganisms across all primate species [40]. Altered gastrointestinal microbiomes can result in increased inflammation [41-42], altered immunosurveillance [44], altered metabolism [45], and directly cause genomic instability and increased cellular proliferation [43]. While isolated on their own each of these factors may not lead to the development of

cancer; together, they increase cellular stress which in turn may lead to the development of cancer.

A branch of evolutionary theory is life history theory. Life history theory studies how natural selection has shaped organisms to take resources from their environment and convert them into offspring [46-48]. Organisms must balance aspects of fitness such as somatic development, maintenance and reproduction [46-48]. These aspects of fitness are known as life-history traits. If resources are allocated to one area, they are unavailable for use in another area and this is known as life-history tradeoffs [46-48]. These tradeoffs may influence the risk of developing cancer. For example, taller males tend to be more reproductively successful; however, they also have a higher risk of developing cancer [69].

There are significant differences between the reproductive patterns of female hunter gatherers and females living in industrialized societies [49-50]. These differences may explain the increasing rates of breast cancer among industrialized women compared with hunter gatherer populations [49]. Females in industrialized societies, in general, undergo menarche at an earlier age, have children at a later age, have fewer children, breast feed for a shorter duration and overall have more menstrual cycles [49-50]. Furthermore, women in industrialized societies have higher rates of obesity [11], have access to hormone replacement therapy [51], birth control [52], and are exposed to numerous xenoestrogens in the environment [53-54]. These factors can influence circulating estrogen levels which in turn may influence the development of breast cancer. A similar pattern can be seen in rates of prostate cancer between men from industrialized societies versus men from non-industrialized societies. Men living in industrialized countries have a 6-10-fold higher incidence of prostate cancer [55-56]. When men from non-industrialized countries migrate to an industrialized country their risk of prostate cancer, over time, increases to levels similar to those of the industrialized population [55-56]. This may be due to multiple factors, but it is believed that access to more calories leads to increased testosterone levels which may influence prostate cancer development and growth [55-56]. In both these instances, moving away from a traditional hunter gatherer lifestyle may influence the risk of developing cancer by affecting hormone levels.

Some mismatches that are often overlooked when it comes to their role in the development of cancer are stress, sleep, and exposure to environmental toxicants. It has been found that stressors early in life [57-58] as well as in adulthood [59] may predispose individuals to developing cancer. Undoubtedly our ancestors were exposed to stress; however, the persistent stress responses induced by our modern environments have multiple negative effects on our health. Stress has been found to inhibit the immune system [60-61], increase inflammation [62], alter our HPA axis [63] and change our DNA methylation patterns [64]. Similarly, modern sleep patterns differ significantly from our ancestors which also may play a role in the

development of cancer [65-66]. Lastly, modern humans are exposed to countless environmental toxicants compared to our hunter gatherer ancestors. The extent that these chemicals affect our bodies and the mechanisms by which they do so are currently unknown; however, it is thought that they may directly alter the tumor microenvironment [67-68]. It is difficult to ascribe causality to these factors since they work through various indirect mechanisms; nonetheless, they do increase systemic stress which in turn could lead to cancer development.

Much about our modern lifestyle is mismatched with how we evolved to live and thrive. These mismatches promote systemic stress which in turn promotes genetic instability and cellular heterogeneity. Cellular heterogeneity may in turn promote the development of cancerous cells. Therefore, by understanding the evolutionary principals underlying cellular evolution and how mismatches promote this, we may be able to find solutions to prevent and reverse these changes. Current cancer research is directed towards the development of treatments for cancer using reductionist methods to target specific mutations in cancer cells. However, these treatments commonly fail [9-10]. This is because tumors are heterogeneous, constantly evolving and routinely become resistant to therapy [3-5]. Therefore, a new paradigm is needed in cancer research. Using an evolutionary framework to view how cancer develops and evolves can help guide us on how to prevent the development of cancer as well as develop new treatments for cancer [6-7]. Evolutionary theory has led to the proposal of multiple different ways to treat cancer such as adaptive therapy [19], ecological therapy [21], phenotypic targeting [22], and using an evolutionary double bind [20]. An evolutionary double bind occurs when two therapies are used in conjunction with one another, and by developing resistance to one therapy, a cancer cell becomes susceptible to the other [20, 72]. While these theories remain largely untested in a clinical setting, they provide promising avenues for future research and clinical studies. The future of cancer prevention and treatment involves looking to the past and our evolutionary heritage.

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