Chapter 5

What's New Among Cancer Etiology Horizon?

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Additional information is available at the end of the chapter

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Abstract

The commonest saying goes as "cancer has no answer," we have really come a long way in that aspect. From being able to detect and diagnose the disease early, effective treatment modalities, improvement in therapeutic outcome and even effective palliative measures. The research focus emphasized upon detecting preventable risk factors. Tobacco a Global culprit is often discussed as the most important risk factor for cancer. Modern day life and with its so-called stress measures are the ones often been blamed without a concrete scientific evidences. Psychological makeup of a person, emotional stress and cellular phones are intricately associated with a modern lifestyle. In this chapter we would be focusing upon the causal relationship between these factors and malignancy with available scientific literature. At the end we would present possible measures to avoid them and any future research areas to be looked upon.

Keywords: cancer, emotional stress, psychological factors, cellular phones, modern lifestyle, habituation, modifiable risk factors

1. Introduction

Cancer is a term coined by the great Greek physician Hippocrates (460–370 BC). He is considered the "Father of Medicine." Hippocrates used the terms carcinos and carcinoma to describe non-ulcer forming and ulcer-forming tumors. Later on Galen (130–200 AD), another Roman physician used the term oncos (Greek for swelling) to describe tumors. Oncos is the root word for oncology or study of cancers.

It has been described in ancient mummies and over several years it has awakened a sense of fear and loss among the Human race. However technology also progressed at a rapid rate and main therapeutic modalities to treat cancer become a triad of surgery, chemotherapy and radiotherapy.

Parallel to these early diagnosis and preventive measures have also been researched in a large scale. This brings us to a domain called etiological factors for cancer. Tobacco has been linked to all head and neck cancers, esophageal cancers, bladder cancer especially, whereas dietary factors are predominant in breast and colon malignancies [1–5]. Interestingly few of the literature dates even more than 50 years back and current data also includes personal sexual behavior, Human papilloma virus infection (HPV) and tobacco in smokers as known risk factors.

These are often mentioned and often discussed issues. Effective strategies in cases of known risk factors have also been developed. Cancer vaccine is one such preventive step. In the case of cervical cancer a preventable vaccine is also been developed and shows promising outcome [6, 7].

Modern day lifestyle also brings along stress in terms if not only physical factors but also emotional issues. Low mood, depression and chronic anhedonia are household terns these days. There have been infrequent reports regarding emotional stress being causative factor for cancer [8–10]. Till date this is an important issue which lacks concrete evidence.

The other modern day risk being cellular phones aka mobile phones. Childhood brain tumors have been linked to it in several reports and it might have some significance. But again a large database and definite evidence is still to come out [11–13].

In this section we would elaborate the available literature related to these two less discussed etiologies of cancer viz. emotional/psychological stress and cellular phones. We would try and find if at all any link exists between them and related issues as per different sites of cancers.

2. Emotional stress

2.1. Introduction

Emotional stress, psychological factors or stressful life events these terms are often used interchangeably. Whatever may be the definition it has long been speculated to be linked to cancer development? The assumption of an association between stress and cancer is popular in the lay public [14]. Long back in 1992 Baghurst et al. described preventable issues but most of them were diet related. There was however a mention about environmental factors but emotional stress was not highlighted. Doll and Peto in 1985 also elaborate the dietary risk factors in different cancers and incidentally stress was highlighted to be a major contributory factor in colon, lung and breast cancers [15].

2.2. Definition

World Health Organization (WHO) defined health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" [16]. With over half a decade and World witnessing several changes the WHO definition also should focus on the ability to adapt and self-manage in face of social, physical, and emotional challenges [17]. With the change in socio-cultural and demographic profile across world social support and emotional stress were linked to chronic diseases. As per American Psychosomatic Society

social support is defined as "information leading the subject to believe that he is cared for and loved, esteemed, and a member of a network of mutual obligations [18]." The article enumerates that social support can protect people during crisis from a wide variety of pathological states like low birth weight to death, from arthritis through tuberculosis to depression, alcoholism, and the social breakdown syndrome. It has bigger implications like reduction in the amount of medication required, acceleration of recovery and compliance to medical regimens prescribed. These data never actually stated development of cancer related to social stress.

2.3. Pathophysiology

Psychological health itself is a difficult domain to assess. Aspects of psychological well-being like self-acceptance, positive relations with others, autonomy, environmental mastery, purpose in life and personal growth were mainly analyzed [19]. All these give a hint of link to chronic disorder and may be malignancy but without much evidence. Long back Evans suggested that the death of a spouse or other close relation could be an important cause of cancer. It was stated that "cancer is a miscarriage of this driving force, under the influence of the collective unconscious which is unrestrained after the patient has given up hope and interest in life (when the objective attachment is broken), that is, after the conscious has given up the struggle with the unconscious" [20]. However the study also could not establish a direct link. There is also no physiological mechanism to account for an increase in the incidence of or mortality from cancer after stressful events has yet to be specified in detail [8]. Loss of an important emotional relationship has been identified in several studies as an event with a high risk of subsequent illness [20–22]. Psychological stress activates the nervous system and the hypothalamic-pituitary-adrenal axis, leading to release of hormones such as glucocorticoids and norepinephrine. It has been shown that stress and the subsequent hormonal dysfunction can cause impairment of DNA repair and hence can suppress the immune system. Additionally, stress may lead to epigenetic silencing: altering DNA methylation and histone acetylation and all these are important in tumor development [23–25].

There is a separate discipline which studies these factors and called as psychoneuroimmunology. The multistep immune reactions are either inhibited or enhanced as a result of previous or parallel stress experiences, depending on the type and intensity of the stressor. As a rule both stressors and depression are associated with the decreased cytotoxic T-cell and natural-killer-cell activities. This further affect processes such as immune surveillance of tumors. This will lead to the events that modulate development and accumulation of somatic mutations and genomic instability [24].

From the time of the ancient Greeks, there has been an interest in the relationship between psychological states and cancer. Epidemiologic evidences have supported the role of biobehavioral risk factors in cancer progression. These are namely social adversity, depression, and stress. This is important both in initiation and progression phases [26, 27].

Early research on central nervous system (CNS) effects on cancer predominantly focused on the following:

a. Down-regulation of the immune response as a potential mediator of impaired surveillance for metastatic spread [27–31].

b. Stress effects on DNA repair [32, 33].

It is to be understood that there is no singular system available in explaining the biological effects of stress pathways on cancer progression. Over the last 10 years, the focus of mechanistic biobehavioral oncology research has broadened and it includes examination of the effects of stress on (a) tumor angiogenesis; (b) invasion and anoikis; (c) stromal cells in the tumor microenvironment, and (d) inflammation [27].

The salient features and how they affect immune system and cancer development or progression is enumerated in **Table 1**.

Biobehavioral factors	Main cause	Pathophysiology	Implications
Cellular immune response in cancer progression [34, 35]	Negative psychosocial states, such as chronic stress, depression, and social isolation	Down-regulation of the cellular immune response, mediated largely by adrenergic and glucocorticoid signaling	1. Depression has also been associated with a poorer cellular immune response to specific antigens in breast cancer 2. One study reported that depressed patients with hepatobiliary carcinoma had lower NK cell numbers and shorter survival compared to their non-depressed counterparts [36]
Angiogenesis and invasion [37–40].	Cancer-related mortality largely results from the spread of cancer cells from the primary tumor to other sites in the body, a process called metastasis. Successful metastatic spread requires several sequential steps, including angiogenesis, proliferation, invasion, embolization, and colonization of a new secondary site	Angiogenesis: this process is tightly controlled by a variety of positive and negative factors secreted by both tumor and host cells in the tumor microenvironment	Stress hormones such as norepinephrine (NE) have been shown to induce production of IL-6 and IL-8 by ovarian cancer and melanoma cells demonstrating effects of stress response pathways on tumor signaling mechanisms
Stress effects on anoikis [41–44]	Anoikis is the normal process of programmed cell death (apoptosis) occurring when anchorage-dependent cells become separated from the ECM. Cancer cells acquire the ability to resist anoikis, thus enhancing their ability to migrate, re-attach, and establish themselves in secondary sites	Catecholamines were found to protect ovarian cancer cells from anoikis, both in vitro and in vivo. These effects were mediated by focal adhesion kinase (FAK), a tyrosine kinase that promotes cell adhesion, which demonstrated increased activation (phosphorylation of pFAKY397) in response to NE. Clinically, elevated levels of pFAKY397 were observed in the tumor tissue of ovarian cancer patients reporting depression and those with higher levels of tumor NE	Ovarian cancer progression

Biobehavioral factors	Main cause	Pathophysiology	Implications
Stromal cells in the tumor microenvironment [43–46]	Tumor growth is to a large extent shaped and promoted or inhibited by signaling between tumor cells and the cells of the microenvironment. In addition to effects of stress hormones on tumor cells, there are marked effects on host cells such as macrophages in the tumor microenvironment	Monocytes are drawn to the tumor microenvironment by tumor-derived chemotactic factors and then differentiate into macrophages. However, under the influence of the pro-inflammatory microenvironment, macrophages are induced to shift from their phagocytic phenotype to a pro-tumor phenotype that produces tumor promoting factors such as VEGF and MMPs, while simultaneously down-regulating the cellular immune response by production of immunosuppressive cytokines such as IL-10 and TGFβ (75–78). TAMs are thus directly involved in promoting angiogenesis, tumor proliferation, invasion, metastases, and down-regulation of adaptive immunity. TAM infiltration is also associated with poorer survival	In ovarian cancer patients, biobehavioral risk factors that have been associated with higher NE levels, such as depression and stress
Glucocorticoid dynamics and cancer progression [47–49]		Glucocorticoids can directly mediate processes promoting tumor growth as well. Cortisol has been shown to stimulate growth of prostate cancer cells (85) and to enhance proliferation of human mammary cancer cells by nearly two-fold	In a murine breast cancer model, social isolation induced an elevated corticosterone stress response, greater tumor burden and alterations in gene expression in metabolic pathways that are known to contribute to increased tumor growth

Table 1. Stress and different pathophysiology.

2.4. Childhood cancers

It is altogether a different entity. Investigators have tried to assess the link between early life stress and development of childhood cancers. It is a unique scenario and in developed countries it is a leading cause of child deaths. Almost half of childhood cancers are diagnosed before 5 years of age and thus the importance of identifying early life risk factors for developing prevention strategies [50–53]. There is a certain physiological aspect also but like in adults the pathways are not very clear.

Large population-based cohort studies from Denmark and Sweden showed a small but statistically significant overall increased risk of childhood cancer was observed among children exposed to bereavement owing to the death of a family member. Exposure was also associated with CNS tumors and leukemia [53].

2.5. Conclusion

There is a definite correlation between stress and immunologic pathways for development of cancer and also for progression. In the clinical literature, lack of perceived social support is a factor that emerges repeatedly in associations with biological variables related to cancer progression, and social isolation has shown similar effects in the preclinical literature. Understanding what it is about social relationships that underlie these associations will be important in future research. Additional questions include the following: How much stress, in terms of thresholds or chronicity, is needed to modulate tumor-related pathways?

Many clinical studies even if prospective have failed to highlight life time stress as causative factor for cancer. The results of a large, prospective, population-based study therefore do not support the hypothesis that life stress, when defined as stressful life events, increases the risk for developing cancer [10].

3. Cellular phones

3.1. Introduction

There are three main reasons why people are concerned that cell phones (also known as "mobile" or "wireless" telephones) might have the potential to cause certain types of cancer or other health problems. Various literature reviews actually gives a very conflicting results. The exposure among pediatric and adult population is different and so as the outcome. As a potential etiology for cancer, cellular phones are yet to be regarded as common pathogens. As Munshi et al. describes "Centuries ago, we advanced from pigeons to postal services as a more modern means to communicate. Since then, communication has made quantum leaps, buoyed by the successes in physics and technology. From crude telephone sets to modern landline, cordless phones and finally cellular phones" [11].

3.2. Background knowledge

Mobile phones first came to use in the early 1990s for professional work-related reasons, and henceforth have attained tremendous growth, becoming able symbols for consumer status and needs. At present, nearly 5 billion people worldwide own cellular phones. India herself can boast of 800 million cellular phone users [54].

Another review by Munshi and Jalali highlighted how the fear of cellular phones and cancer develop. A decade ago a man in Florida, US sued a cell phone company alleging it lead to brain tumor in his wife [55]. The scientific evidence shows that mobile phones emit electromagnetic radiation (radiofrequency, RF) that is essentially non-ionizing. (frequencies between 300 MHz and 300 GHZ) [56–58]. The specific absorption rate (SAR) measures the energy dose that subjects exposed to RF absorb and is expressed in power (watts) by tissue mass (kilograms) [W/kg]. Effects of this dose deposition by use of cellular phones, however, take long to manifest. In some cases, this duration may be 10 years or more.

In general public there can be 3 reasons of concern:

a. Cell phones emit radiofrequency energy (radio waves), a form of non-ionizing radiation, from their antennas. Tissues nearest to the antenna can absorb this energy.

b. The number of cell phone users has increased rapidly. As of December 2014, there were more than 327.5 million cell phone subscribers in the United States, according to the Cellular Telecommunications and Internet Association. This is a nearly threefold increase from the 110 million users in 2000. Globally, the number of subscriptions is estimated by the International Telecommunications Union to be 5 billion.

c. Over time, the number of cell phone calls per day, the length of each call, and the amount of time people use cell phones have increased. However, improvements in cell phone technology have resulted in devices that have lower power outputs than earlier models [59].

It is to be noted that cell phones are often held tightly against the head. Electromagnetic radiation is governed by an interesting law known as the inverse square law. This essentially means that if we increase distance from the source by a factor of 2, the exposure gets reduced by 1/4th. It is for this reason, that distance from the device is a critical factor which decides the exposure received from a particular device. It is for the same reason that, if indeed a true risk exists, children would be at particular risk because their skulls are thinner. Also the cumulative lifetime exposure of children to cell phones would likely be greater than the exposure of current adults [11].

3.3. Clinical studies

Most of the work in cancer etiology and cellular phones has been based on brain tumors and parotid/salivary gland tumors because of the vicinity between these structures and cellular phone when used by an individual. Among brain tumors also most studies linked to glioma, meningioma and acoustic neuroma/schwannomas [11, 55].

There has been a meta-analysis published in JCO in 2009 about cellular phones and cancer risk. Myung et al. have selected initial 465 articles meeting their criteria and finally 23 case-control studies, which involved 37,916 participants were chosen. They found that a significant positive association (harmful effect) was observed in a random effects meta-analysis of eight studies using blinding, whereas a significant negative association (protective effect) was observed in a fixed-effects meta-analysis of 15 studies not using blinding. Mobile phone use of 10 years or longer was associated with a risk of tumors in 13 studies reporting this association (odds ratio = 1.18; 95% CI, 1.04–1.34) [60].

In reply to the above Stang et al. Criticized these random effects and have pointed out flaws related to the methodology. They have also highlighted their own data from uveal melanoma. After their initial case report they carried out case-control study on uveal melanoma focusing on mobile phone use and used the same detailed exposure assessment as the Interphone study used. The authors could not corroborate their previous results that showed an increased risk of uveal melanoma among regular mobile phone users. They accepted that probabilistic multiple error sensitivity analyses to evaluate the potential of exposure misclassification bias and selection bias did not explain the null result [61, 62].

The Interphone study group published the outcomes of an interview-based, case-control study with 2708 glioma and 2409 meningioma cases and matched controls. The study was conducted in 13 countries using a common protocol. The result of the study suggested that no increase in risk of glioma or meningioma was observed with use of mobile phones [63]. The cell phone companies faced these challenges and as of now they claim that Cell phone technology too is rapidly advancing and the electromagnetic exposure is progressively less with newer phones [64].

The World Health Organization (WHO) set up an expert panel to evaluate the effect of cell phones on the human body. On May 31, 2011 the expert panel said that cell phones might possibly cause side effects. The International Agency for research on Cancer (IARC) panel found cell phones to be "possibly carcinogenic," and stated that heavy cell phone use might or might not cause glioma [65]. Further in 2015 it was declared in a multicentric study that cell phone radiation can cause brain tumors and this to be categorized as probable human carcinogen category 2A. This study stated that previous IARC classification of Group 2B (possible) carcinogen in 2011 should be reclassified as a Group 2A (probable) carcinogen [12].

The basis of the above was another large scale epidemiologic study called CERENAT study which was a French case-control study of cases ≥16 years of age diagnosed between June 2004 and May 2006 included 253 glioma and 194 meningioma cases with two age- and gender-matched controls per case selected between 2005 and 2008. They included Potential confounders such as the level of education, smoking, alcohol consumption, and occupational exposures to pesticides, extremely low frequency electromagnetic fields (ELF-EMF), radiofrequency electromagnetic fields (RF-EMFs), and ionizing radiation. Risks of glioma were reported for heavy mobile phone use (≥896 cumulative hours of use). When heavy mobile phone use was examined by years since first use, glioma risk increased from >1 year since first use, to >2 years and to >5 years, OR 2.89, [95% confidence interval (CI) 1.41–5.93], OR 3.03, (95% CI 1.47–6.26), and OR 5.30, (95% CI 2.12–13.23), respectively. There was a borderline significant risk for glioma in the temporal lobe. This study also suggested risk for meningioma but lesser than glioma [66].

Interestingly these EM radiations can both initiate and promote tumor progression. In an Australian study of regional hospital-based data for the years 2000–2008, Dobes et al. stated, a significant increasing incidence in glioblastoma multiforme (GBM) was observed in the study period particularly after 2006 [67]. An increasing incidence of brain tumors during 2003–2012, 41.2% among men and 46.1% in women has been noted in Denmark, cases of GBM nearly doubled in the previous 10 years [68].

3.4. Precautions

Munshi and Jalali have beautifully highlighted how we can take few precautions. (1) Use the cell phone whenever it is really needed. For most routine work and casual talks, use the regular landline connection. (2) Discourage children from excessive use of cell phones.

(3) Whenever possible, use a wired ear piece connected to the cell phone. (4) Avoid cell phone use when the signal is weak. (5) Consider alternating between left and right ear while talking on cell phone. (6) Use texting (SMS) instead of calling when possible [55]. Morgan et al. also stated that until further evidence is available, it is prudent to follow the ALARA standard used in pediatric radiology. The ALARA approach would require hardware and software designers to create proximity sensors and embed flash notices regarding simple advisories about safer use within devices [12].

3.5. Conclusion

The data regarding cellular phone usage and cancer risk is ever emerging. We have some progress towards stronger association as IARC classification changed. As time advances newer and more mature results will come up. At the same time it is also true that a billionaire cellular phone Industry will also come up with safer devices. We will also need prospective data as the major limitation of epidemiological studies addressing the health effects of mobile phone use is related to exposure assessment. These limitations are inherent in case-control studies [69]. Borrowing the lines from Munshi et al. "it may be some time before we know if the friendly gizmos in our hands have the ability to cause aggressive tumors, for the time being, you have the free choice—to talk or not to talk" [11].

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References

[1] Armstrong B, Doll R. Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. International Journal of Cancer. 1975;**15**:617-631

[2] Wynder EL, Bross IJ, Feldman RM. A study of the etiological factors in cancer of the mouth. Cancer. 1957;**10**:1300-1323

[3] Wynder EL, Bross IJ. A study of etiological factors in cancer of the esophagus. Cancer. 1961;**14**:389-413

[4] Gandhi AK, Kumar P, Bhandari M, Devnani B, Rath GK. Burden of preventable cancers in India: Time to strike the cancer epidemic. Journal of the Egyptian National Cancer Institute. 2017;**29**:11-18

[5] Shah A, Malik A, Garg A, Mair M, Nair S, Chaturvedi P. Oral sex and human papilloma virus-related head and neck squamous cell cancer: A review of the literature. Postgraduate Medical Journal. 2017 Aug 4 pii: postgradmedj-2016-134603

[6] Jindal HA, Kaur A, Murugan S. Human Papilloma Virus vaccine for low and middle income countries: A step too soon? Human Vaccines & Immunotherapeutics. 2017 Aug 28:1-3. DOI: 10.1080/21645515.2017.1358837 [Epub ahead of print]

[7] Huh WK, Joura EA, Giuliano AR, Iversen OE, de Andrade RP, Ault KA. Final efficacy, immunogenicity, and safety analyses of a nine-valent human papillomavirus vaccine in women aged 16-26 years: A randomised, double-blind trial. Lancet. 2017 Sep 5. pii: S0140-6736(17)31821-4. DOI: 10.1016/S0140-6736(17)31821-4 [Epub ahead of print]

[8] Jones DR, Goldblatt PO, Leon DA. Bereavement and cancer: Some data on deaths of spouses from the longitudinal study of Office of Population Censuses and Surveys. British Medical Journal (Clinical Research Ed.). 1984;**289**:461-464

[9] Taylor C, Trowbridge P, Chilvers C. Stress and cancer surveys: Attitudes of participants in a case-control study. Journal of Epidemiology and Community Health. 1991;**45**:317-320

[10] Bergelt C, Prescott E, Grønbaek M, Koch U, Johansen C. Stressful life events and cancer risk. British Journal of Cancer. 2006;**95**:1579-1581

[11] Munshi A. Cellular phones: To talk or not to talk. Journal of Cancer Research and Therapeutics. 2011;**7**:476-477

[12] Morgan LL, Miller AB, Sasco A, Davis DL. Mobile phone radiation causes brain tumors and should be classified as a probable human carcinogen (2A) (review). International Journal of Oncology. 2015;**46**:1865-1871

[13] McKinney PA. Brain tumours: Incidence, survival, and aetiology. Journal of Neurology, Neurosurgery, and Psychiatry. 2004;**75**(Suppl 2):ii12-17

[14] Baghurst KI, Baghurst PA, Record SJ. Public perceptions of the role of dietary and other environmental factors in cancer causation or prevention. Journal of Epidemiology and Community Health. 1992;**46**:120-126

[15] Doll R, Peto R. The causes of cancer: Quantitative estimates of avoidable risk of cancer in the United States today. Journal of the National Cancer Institute. 1981;**66**:1193-1265

[16] Callahan D. The WHO definition of 'health'. Studies—Hastings Center. 1973;**1**:77-88

[17] Nobile M. The WHO definition of health: A critical reading. Medicine and Law. 2014; **33**:33-40

[18] Cobb S. Presidential Address-1976. Social support as a moderator of life stress. Psychosomatic Medicine. 1976;**38**:300-314

[19] Ryff CD. Happiness is everything, or is it? Explorations on the meaning of psychological well-being. Journal of Personality and Social Psychology. 1989;**57**:1069-1081

[20] Evans E. A Psychological Study of Cancer. New York: Dodd Mead and Co; 1926

[21] LeShan L. An emotional life history pattern associated with neoplastic disease. Annals of the New York Academy of Sciences. 1966;**125**:780-793

[22] Muslin HL, Gyarfas K, Pieper WJ. Separation experience and cancer of the breast. Annals of the New York Academy of Sciences. 1966;**125**:802-806

[23] Kiecolt-Glaser JK, Glaser R, Williger D, et al. Psychosocial enhancement of immunocompetence in a geriatric population. Health Psychology. 1985;**4**:25-41

[24] Reiche EM, Nunes SO, Morimoto HK. Stress, depression, the immune system, and cancer. The Lancet Oncology. 2004;**5**:617-625

[25] Hunter RG. Epigenetic effects of stress and corticosteroids in the brain. Frontiers in Cellular Neuroscience. 2012;**6**:18

[26] Brock AJ. Greek Medicine: Being Extracts Illustrative of Medical Writers from Hippocrates to Galen. London, England: JM Dent and Sons; 1929

[27] Lutgendorf SK, Sood AK. Biobehavioral factors and cancer progression: Physiological pathways and mechanisms. Psychosomatic Medicine. 2011;**73**:724-730

[28] Levy S, Herberman R, Lee J, Whiteside T, Kirkwood J, McFeeley S. Estrogen receptor concentration and social factors as predictors of natural killer cell activity in early-stage breast cancer patients. Natural Immunity and Cell Growth Regulation. 1990;**9**:313-324

[29] Levy S, Herberman R, Lippman M, D'Angelo T, Lee J. Immunological and psychosocial predictors of disease recurrence in patients with early-stage breast cancer. Behavioral Medicine. 1991;**17**:67-75

[30] Levy S, Herberman R, Maluish A, Schlein B, Lippman M. Prognostic risk assessment in primary breast cancer by behavioral and immunological parameters. Health Psychology. 1985;**4**:99-113

[31] Levy SM, McCabe PM, Schneiderman N, Field TM, Skyler JS, editors. Stress, Coping and Disease: Behavioral and Immunological Host Factors in Cancer Risk. Hillsdale, NJ: Lawrence Erlbaum Associates; 1991. p. 237-253

[32] Glaser R, Thorn B, Tarr K, Kiecolt-Glaser J, D'Ambrosio S. Effects of stress on methy-transferase synthesis: An important DNA repair enzyme. Health Psychology. 1985;**4**:403-412

[33] Kiecolt-Glaser JK, Stephens RE, Lipetz PD, Speicher CE, Glaser R. Distress and DNA repair in human lymphocytes. Journal of Behavioral Medicine. 1985;**8**:311

[34] Blomberg BB, Alvarez JP, Diaz A, Romero MG, Lechner SC, Carver CS, Holley H, Antoni MH. Psychosocial adaptation and cellular immunity in breast cancer patients in the weeks after surgery: An exploratory study. Journal of Psychosomatic Research. 2009;**67**:369-376

[35] Sephton SE, Dhabhar FS, Keuroghlian AS, Giese-Davis J, McEwen BS, Ionan AC, Spiegel D. Depression, cortisol, and suppressed cell-mediated immunity in metastatic breast cancer. Brain, Behavior, and Immunity. 2009;**23**:1148-1155

[36] JL GDA, Gamblin TC, Olek MC, Carr BI. Depression, immunity, and survival in patients with hepatobiliary carcinoma. Journal of Clinical Oncology. 2007;**25**:2397-2405

[37] Fidler IJ. The pathogenesis of cancer metastasis: The 'seed and soil' hypothesis revisited. Nature Reviews. Cancer. 2003;**3**:453-458

[38] Folkman J. What is the evidence that tumors are angiogenesis dependant? Journal of the National Cancer Institute. 1990;**82**:4-6

[39] Folkman J, Klagsbrun M. Angiogenic factors. Science. 1987;**235**:442-447

[40] Senger DR, Galli SJ, Dvorak AM, Perruzzi CA, Harvey VS, Dvorak HF. Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. Science. 1983; **219**:983-985

[41] Shanmugathasan M, Jothy S. Apoptosis, anoikis and their relevance to the pathobiology of colon cancer. Pathol Int. Apr 2000;**50**(4):273-279

[42] Yawata A, Adachi M, Okuda H, et al. Prolonged cell survival enhances peritoneal dissemination of gastric cancer cells. Oncogene. 1998;**16**:2681-2686

[43] Pollard JW. Tumour-educated macrophages promote tumour progression and metastasis. Nature Reviews. Cancer. 2004;**4**:71-78

[44] Sica A, Allavena P, Mantovani A. Cancer related inflammation: The macrophage connection. Cancer Letters. 2008;**267**:204-215

[45] Sica A, Rubino L, Mancino A, et al. Targeting tumour-associated macrophages. Expert Opinion on Therapeutic Targets. 2007;**11**:1219-1229

[46] Sica A, Schioppa T, Mantovani A, Allavena P. Tumour-associated macrophages are a distinct M2 polarised population promoting tumour. European Journal of Cancer. 2006;**42**:717-727

[47] Zhao XY, Malloy PJ, Krishnan AV, et al. Glucocorticoids can promote androgen-independent growth of prostate cancer cells through a mutated androgen receptor. Nature Medicine. 2000;**6**:703-706

[48] Simon WE, Albrecht M, Trams G, Dietel M, Holzel F. In vitro growth promotion of human mammary carcinoma cells by steroid hormones, tamoxifen, and prolactin. Journal of the National Cancer Institute. 1984;**73**:313-321

[49] Elenkov IJ. Glucocorticoids and the Th1/Th2 balance. Annals of the New York Academy of Sciences. 2004;**1024**:138-146

[50] Anderson LM. Environmental genotoxicants/carcinogens and childhood cancer: Bridgeable gaps in scientific knowledge. Mutation Research. 2006;**608**:136-156

[51] Kaatsch P. Epidemiology of childhood cancer. Cancer Treatment Reviews. 2010;**36**:277-285

[52] Parkin DM, Whelan S, Ferlay J, et al. Cancer Incidence in Five Continents VIII. Vol. 155. Lyon, France: IARC Scientific Publications (IARC); 2002

[53] Momen NC, Olsen J, Gissler M, Cnattingius S, Li J. Early life bereavement and childhood cancer: A nationwide follow-up study in two countries. BMJ Open. 2013;**3**(5):e002864. DOI: 10.1136/bmjopen-2013-002864

[54] Hoskote SS, Kapdi M, Joshi SR. An epidemiological review of mobile telephones and cancer. The Journal of the Association of Physicians of India. 2008;**56**:980-984

[55] Munshi A, Jalali R. Cellular phones and their hazards: The current evidence. National Medical Journal of India. 2002;**15**:275-277

[56] Heynick LN, Johnston SA, Mason PA. Radio frequency electromagnetic fields: Cancer, mutagenesis, and genotoxicity. Bioelectromagnetics. 2003;**6**:S74-100

[57] Chang SK, Choi JS, Gil HW, Yang JO, Lee EY, Jeon YS, et al. Genotoxicity evaluation of electromagnetic fields generated by 835-MHz mobile phone frequency band. European Journal of Cancer Prevention. 2005;**14**:175-179

[58] Hardell L, Sage C. Biological effects from electromagnetic field exposure and public exposure standards. Biomedicine & Pharmacotherapy. 2008;**62**:104-109

[59] Available from: https://www.cancer.gov/about-cancer/causes-prevention/risk/radiation/cell-phones-fact-sheet. [Accessed: May 2017]

[60] Myung SK, Ju W, McDonnell DD, Lee YJ, Kazinets G, Cheng CT, et al. Mobile phone use and risk of tumors: A meta-analysis. Journal of Clinical Oncology. 2009;**27**:5565-5572

[61] Stang A, Anastassiou G, Ahrens W, et al. The possible role of radiofrequency radiation in the development of uveal melanoma. Epidemiology. 2001;**12**:7-12

[62] Stang A, Schmidt-Pokrzywniak A, Lash TL, et al. Mobile phone use and risk of uveal melanoma: Results of the risk factors for uveal melanoma case-control study. Journal of the National Cancer Institute. 2009;**101**:120-123

[63] Interphone Study Group. Brain tumour risk in relation to mobile telephone use: Results of the INTERPHONE international case-control study. International Journal of Epidemiology. 2010;**39**:675-694

[64] Pope L, Silva P, Almeyda R. Phone applications for the modern day otolaryngologist. Clinical Otolaryngology. 2010;**35**:350-354

[65] Available from: http://www.iarc.fr/en/media-centre/pr/2011/pdfs/pr208_E.pdf [Accessed: 2011 Aug 2]

[66] Coureau G, Bouvier G, Lebailly P, et al. Mobile phone use and brain tumours in the CERENAT case-control study. Occupational and Environmental Medicine. 2014;**71**:514-522

[67] Dobes M, Khurana VG, Shadbolt B, Jain S, Smith SF ea. Increasing incidence of glioblastoma multiforme and meningioma, and decreasing incidence of Schwannoma (2000-2008): Findings of a multicenter Australian study. Surgical Neurology International. 2011;**2**:176

[68] The Danish Cancer Society. The Increase in New Cases of Aggressive Brain Cancer. http://www.cancer.dk/Nyheder/nyhedsartikler/2012kv4/Kraftigstigningihjernesvulster.html. [Accessed: 22-09-2014]

[69] Auvinen A, Toivo T, Tokola K. Epidemiological risk assessment of mobile phones and cancer: Where can we improve? European Journal of Cancer Prevention. 2006;**15**:516-523