Review article
Ανασκόπηση

Substance abuse and cancer

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Substance abuse is a health problem with serious psychological and psychiatric dimensions and multiple social and economic consequences. Cancer is a disease that threatens not only life and physical integrity but mental health as well. Oncology patients suffer from mental disorders in high rates, especially from depression and anxiety. The role of substance abuse in the pathogenesis of cancer is studied systematically, since there are research data supporting the mutagenic effects of certain substances. It has been supported that a possible dysregulation of the immune system is linked to the oncogenic processes induced by substances of abuse. Specifically, opioids are the first addictive substances that have been identified as oncogenic factors. However, conflicting results have been offered by experimental animal studies, which showed that opioids, such as morphine, depending on the dosage administered, may not only enhance the process of tumor growth, but also inhibit it. Additionally, research data indicate that the use of cannabis may be associated with cancer, either as an independent factor or in relation to other mutagenics, although it is not yet clear to which extent these effects may be connected to the disease, especially once the consumption of tobacco and alcohol by these patients are taken into account. However, it has been argued that certain cannabinoids may have biological –anticancer– activities which could be used therapeutically without being accompanied by the corresponding 9-tetrahydrocannabinol psychoactive effects. It is well known that alcohol is a risk factor for developing head and neck cancer, and epidemiological studies indicate that the higher the consumption of alcohol, the more mortality due to cancer increases. In addition, it is suggested that there is no safety level for alcohol consumption regarding the risk of developing cancer; that is even a minimum daily consumption is associated with the occurrence of certain types of cancer. Specific components have been identified in tobacco, which are considered to be carcinogenic and responsible for tumor development in various sites. Moreover, complicated psychiatric problems arise due to substance abuse in cancer patients, either in the context of pain treatment, or under pre-existing dependence. The rational use of opioid analgesics, when it is medically required as suggested by the health professionals specialized in the treatment of acute pain in cancer patients, could be a therapeutic option. Substance abuse reduces treatment compliance, worsens cancer prognosis and seems to be a negative factor for the quality of life of these patients. Current literature highlights the importance of appropriate psychiatric interventions to address substance abuse in cancer patients.

Key words: Substances abuse, alcohol, smoking, cancer, immune system, pain.

Introduction

The use and the abuse of addictive substances –legal and illegal– are among the greatest public health problems of the developed world and may lead to serious social complications. The use of alcohol and other substances has been associated with reduced productivity, absence from work and accidents which may lead to financial hardship.[1] Furthermore, the significant health problems that accompany substances abuse lead to a serious burden on the health system, especially in countries such as Greece, where the health system is still in development and maturation process. The comorbidity of mental disorders with other medical conditions in patients with substance abuse disorders constitutes a major health problem that requires targeted medical interventions and the securing of financial resources.

Cancer is the most common cause of death after heart disease. These patients experience high levels of stress and –depending on each person's vulnerability– they suffer from mental disorders at high rates such as depression and anxiety disorders.[2] Cancer is not only a life-threatening disease, but it also constitutes a psychotraumatic factor that may trigger negative feelings and affect functionality.

Many environmental factors have been studied and implicated for their mutagenic action.[3,4] Current research offers some scientific evidence supporting the link of addictive substances with cancer.[5] Moreover, both these serious health problems are investigated in the light of psychosocial issues which result from the substance abuse by cancer patients, either in the context of pain management, or under a preexisting psychiatric history of dependency.

The role of addictive substances in pathogenesis of cancer

Opioids

Opioids are the first substances which were identified as oncogenetics. Research studies support that opioid receptors, mainly the μ-receptors, are associated with the increase and growth of cancer cells and the enhancement of angiogenesis and metastasis. These data refer to the endogenous opioids but also to the exogenous opioids which are administered to cancer patients for pain management.[6,7] It is under question if drugs which act as antagonists of opioid receptors could inhibit, in some degree, the carcinogenesis process.[8]

Heroin

Early cytogenetic studies show that the use of heroin affects and leads to significant changes in the chromosomes. The withdrawal from heroin use and the admission into a drug treatment program are associated with a significant reduction of chromosomal damage within a year.[9] Indeed, studies with newborns of mothers addicted to heroin showed that the chromosome alterations were six to seven times more compared to the control group with newborns of normal mothers. Previous studies showed a high prevalence of approximately 10% of these alterations in cells that were studied prenatally and postpartum in mothers who had used heroin or were in methadone treatment program.[10] Similar findings were reported in primates that received heroin. Chromosome damage of these newborns was ten times more than newborns of healthy animals.[11] A study showed the association of heroin with carcinogenesis. Specifically, it showed an unexpected increase in the CNS of M2 protein in patients with acute myeloid leukemia which is associated with heroin addiction in the past.[12] In a recent study, 44,000 patients attended a program for heroin over 10 years. In this program, high death rates from cancer were reported, which according to the authors may be related to the increased frequency of infections due to immunosuppression and with the significant consumption of tobacco and alcohol.[13] However, it should be considered that the earliness of deaths among heroin users might not permit a full research regarding its influence in the development of neoplasms.

Morphine

Morphine is a derivative of heroin and is mainly used for the treatment of pain. In *in vivo* studies (animal studies), its impact on the chromosome was confirmed, while it wasn't possible to confirm these findings by in vitro studies. Morphine is classified as a co-mutagenic and it is supported that it could act in a long term through inhibition of copying or in relation to procedures of the repair of mutations leading to the conversion of temporary changes in permanent mutations.[14] In animal studies, it was shown that morphine does not cause the development of new tumors but increases the growth of existing neoplasms, thus reducing the life of the animal.[15] However, research data are conflicting, since there

are both *in vivo* and *in vitro* studies which support not only the enhancement but also the reduction of tumors. It seems that the difference in the results is associated with the administered dose of this opioid. Specifically, larger doses for significant periods of time may limit the tumor's growth, while lower doses may be associated with adverse effects.[16] Moreover, the immunosuppressive activity and the effect of morphine in cell apoptosis may be involved in the biological pathways that lead to carcinogenesis.[17,18]

Codeine

Due to its widespread and systematic use as an analgesic, codeine has been included in the substances for evaluation by the National Cancer Institute and the FDA in the United States' national research program for the effects of toxic substances on public health. No evidence was found regarding carcinogenesis, however it is considered to belong to the substances that may potentially cause cancer in laboratory animals.[19,20]

Cocaine

Cocaine is known for its teratogenic properties, the disruption of the neurotransmitters function, and its concomitant alterations in brain structures such as cortical areas.[21] Furthermore, cocaine is associated with severe perinatal lesions and with abortions.[22] In laboratory animals it causes severe liver damage accompanied by significant changes in DNA.[23] Although the carcinogenetic properties of cocaine have not been established, the automated electronic evaluation [Computer Automated Structure Evaluation (CASE)] classifies cocaine among carcinogenic agents. This is an advanced artificial intelligence program that identifies molecular infrastructure which is responsible for different biological activities.[24] Furthermore, the adulteration of cocaine with levamisole, a powerful and toxic anti-inflammatory and anti-cancer agent, causes many side effects such as agranulocytosis, while studies estimating the danger of mixing the two substances are in progress.[25] Additionally, the cocaine use has been found to reduce the response to the administration of chemotherapeutic agents, such as imatinib in patients with chronic myeloid leukemia, probably because of cocaine's effect on cytochrome P450.[26]

Cannabis

Cannabis, also known as marijuana, originates from the plant Cannabis Sativa and is used as a psychoactive substance, as well as a pharmaceutical agent. The component with the principal psychoactive activity is 9-tetrahydrocannabinol which is one of the 483 known components. Eighty three are cannabinoids.[27] Research data indicate that cannabis smoking may be involved in carcinogenesis, either as an independent factor, or in connection with other mutagens, especially in studies concerning the respiratory and gastrointestinal system of young adults.[28] Indeed, important histopathologic and molecular changes have been observed in the bronchial epithelium of systematic hashish smokers. In particular, in systematic smokers, more histopathologic lesions were identified compared to the control group which included non-smokers.[29] However, from a recent meta-analysis of 6 case-control studies which included 2,150 patients who suffered from lung cancer, only some indications were found as concerns the association of lung cancer with chronic cannabis, taking into consideration the tobacco smoking and the severity of cannabis abuse,[30] Although research data support the adverse effects of cannabis in the respiratory system, it is not clear yet to what extent these effects are associated with cancer.[31] Additionally, the findings of epidemiological studies regarding the risk of head and neck cancer are contradicting, especially after controlling for tobacco and alcohol use in these patients.[32] Similar studies have also been conducted as regards other cancer types, such as the testicular cancer. A study indicated that among the oncological patients, those who had a history of cannabis use were twice as like to develop certain histological types of cancer with worse prognosis, compared to patients who had no relevant history.[33] However, some preclinical animal studies showed that certain cannabinoids such is cannabidiol (CBD), may have biological effects, which can be used therapeutically as anti-cancer, anti-inflammatory and analgesic substances, without 9-tetrahydrocannabinol psychoactive effect. The anticancer effects of cannabinoids are related to a variety of mechanisms such as the reduction of apoptosis in healthy cells, the inhibition of proliferation in cancer cells, and the minimization of tumor angiogenesis and metastasis process. In particular, *in vitro* studies of breast and lung cancer cells, it has been argued that CBD through its action in receptors, such as the receptor cannabinoid type 1(CB1) and the intercellular adhesion molecule-1 (ICAM-1 is associated with the immune system) may restrict the survival of cancer cells, with small effect on health cells, while it reduces the migration of malignant cells. Moreover, there is strong evidence from *in vitro* studies that this specific cannabinoid increases the chemo-

preventive action of certain drugs, and helps the uptake of chemotherapeutic agents into tumor cells.[34]

Alcohol

It is known that the abuse and alcohol dependence is one of the greatest and most intractable public health problems with high costs and serious social effects. The degree of consumption and the frequency of abuse are related to a variety of physical and psychological problems. Furthermore, according to the World Health Organization it is one of the five major risk factors internationally associated with disease, disability and death. Additionally, it constitutes a causative agent for more than 200 diseases, with cancer among them.[35] Indeed, there is evidence that the prenatal fetal exposure to alcohol increases in adulthood the probability of dependence behaviors through mechanisms that cause changes in neurotransmitters' function and eventually neurophysiological changes with adverse effects on learning processes.[36] In this context it appears that early brain exposure to alcohol during its primary development stages increases indirectly carcinogenesis, since it is a risk factor for alcoholism.

A review of genetic epidemiology studies of head and neck cancer showed that these types of cancer are associated with polymorphisms in the alcohol metabolism genes. Specifically, they are associated with three variants of ADH (Alcohol dehydrogenase) gene, which controls the metabolism of ethanol. This risk can be modified by the genes that control ADH, especially polymorphisms ADH1B and ADH1C, which oxidizes ethanol to its carcinogenic metabolite, acetaldehyde.[37]

Epidemiological studies indicate that the higher the consumption of alcohol, the greater the mortality from cancer, and furthermore that there is no security level in alcohol use in relation to the risk of cancer development. Even a minimum daily consumption is associated with the occurrence of certain types of cancer.[38]

It is well known that alcohol is a risk factor for head and neck cancer, especially in the oral cavity, pharynx, larynx and esophagus.[39] The results of various studies show that stopping alcohol consumption is associated with a reduced risk of cancer development in the larynx and pharynx. A study concludes that for the heavy drinkers 35 years of discontinuing consumption are required, so that the relative risk would become equal to that of individuals' who do not consume alcohol. However, it is noteworthy that significant reduction of risk is recorded in a short time, which demonstrates the major importance of discontinuing alcohol in order to prevent cancer.[40] Also, alcohol consumption is a risk factor for various other cancer types; such are in upper digestive tract, liver, bowel and in breast.[41–43] Indeed, an even small dose of ethanol increases the risk for breast cancer. Specifically, moderate alcohol consumption is found to increase the risk for breast cancer by 4%, while heavy consumption increases it by 40–50%. It has been suggested that alcohol increases the levels of estrogen and thus enhances carcinogenic effect of hormones in mammary gland. Also, the role of acetaldehyde and some epigenetic changes that involve methyl-1-transferase which affect the life cycle cell are studied.[44] Prevention strategies should be designed to include early detection of alcohol abuse in women in order to reduce the risk for breast cancer. A significant proportion of depressive women abuse alcohol and that may not be recognized by mental health professionals.[45] Furthermore, the results of a recent meta-analysis support the existence of a casual relationship between heavy alcohol consumption and an increased risk for colon cancer, and also provide further evidence for the association between moderate alcohol intake and a relative risk for colon cancer. Nevertheless, many issues remain unsolved, including the quantification of consumption, since there are indications of risk even for mild consumption (a drink per day). However, moderate (2–3 drinks/day) alcohol consumption was found to increase by 21% the development of cancer and heavy one (>4 drinks/day, which is equivalent to >50 gr/day of ethanol) is associated with 52% increased risk for colorectal cancer.[46] The aforementioned findings along with the fact that a great number of women and especially men consume alcohol in a regular basis as well as with the high global incidence of colorectal cancer (particularly in developed countries) are of great significance due to their impact on public health. Abstinence from alcohol should be included in prevention strategies for colon cancer.

Smoking

In tobacco, specific components are identified which are considered to be carcinogenic and responsible for the development of disease in various locations on the head, neck, lung, prostate and kidney.[47] Indeed, a total of 30% of cancers are thought to be related to smoking and tobacco consumption.[48] Smoking has been implicated in the development of lung cancer and studies have explored the correla-

tion of specific histological types such as adenocarcinoma which is related to lower diversification in smokers.[49] In fact, lung cancer patients who smoke report higher levels of stress in comparison with cancer patients suffering from any other type of cancer, which is associated with strong feelings of guilt and shame about their behavior and the casual relationship of this behavior with lung cancer.[50]

Abuse of addictive substances in cancer

The use of addictive substances has been studied in adult patients who have survived from cancer that appeared in childhood. One study suggested that cancer survivors, who were diagnosed in older age, were at greater risk for substance abuse and the appropriate psychiatric interventions could reduce this risk.[51]

The use of opioids analgesics to control pain in cancer

Cancer is accompanied by serious and persistent physical complaints including chronic pain which is an important negative prognostic factor for survival in cancer patients.[52] The use of opioids as analgesics to treat cancer is a common treatment option. However, various clinical issues arise related to their administration, particularly in terminally ill patients. Frequently, due to their concern that their patients may develop dependence, doctors avoid to administer analgesics to such an extent that the patients cannot experience the therapeutic benefits of analgesia. Moreover, the patient's relatives, based on the same rationale, may also feel concerned and thus may reject the idea of their family member using opioids. Therefore, the fear of stigma may influence and hinder medical care.[53]

Additionally, the use of opioids for pain treatment and specifically acute pain or pain at terminally ill patients is associated with lower risk for developing abuse behaviors. In contrast, the use of these drugs in chronic pain and especially in patients with substance abuse history, increase the relative risk, which generally is identified in 8 to 17% of cancer patients who receive opioids for treating chronic pain.[54] When medically necessary, the careful use of opioids analgesics for acute pain management in cancer patients is suggested.[55] The appropriate education and training of healthcare professionals is necessary in order to ensure an integrative medical approach, free from prejudiced beliefs.[56]

Alcohol abuse in cancer patients

Alcohol abuse is a risk factor for certain cancers types; such are head and neck cancer. Some of the patients continue to abuse alcohol even after their cancer's diagnosis and that is a frequent practice with bad consequences both in the quality of life and in the survival of these patients.[57] Indeed, a study which assessed the habits of cancer patients with head–cervical cancer according to alcohol, found that half of these patients continued to consume alcohol.[58] Psychiatric interventions in these patients aiming at psycho-educating them regarding the possible consequences of alcohol use, as well as treating depressive symptoms, that often appear in cancer patients who abuse alcohol, could lead to the reduction of alcohol intake, with beneficial results in the prognosis of cancer.[59]

Tobacco use in cancer patients

Many patients despite being diagnosed with cancer continue to smoke or relapse quickly in case they had quit smoking. Specifically, a study which recorded the behavior of smoker patients with non-small cell lung cancer during a four-year period found that only almost 40% of them had permanently quit smoking in the first two years.[60] It has been observed that critically ill patient quit smoking more frequently and more constantly than those with less serious disease. Indeed, in a study for smoking cessation of patients with head and neck cancer, patients who were treated with a surgery as laryngectomy, had significantly higher rates of abstinence from smoking compared with those who received radiotherapy.[61] Therefore, several factors may influence smoking cessation and the duration of abstinence in cancer patients, such as the stage of the disease and the treatment selected. Moreover, it has been suggested that the time period during the diagnosis of cancer could be used in order to implement the appropriate interventions, since the high motive and the therapeutic relationship may facilitate smoking cessation. Also, it is required to address possible problems that follow smoke cessation, such as depression and weight gain. The use of drug therapies, such as nicotine replacement therapy (e.g., skin patches or nicotine gum) and problem solving training may be used in combination to achieve the best possible therapeutic result.[62]

Conclusions

The abuse of legal and illegal substances through direct and indirect mechanisms increases inflammatory activity at a molecular level.[63] Meanwhile, evidence from epidemiological, preclinical and clinical studies, suggest that dysregulated inflammatory activity plays a central role in a variety of chronic diseases, including cancer. These inflammatory processes may be triggered by a number of environmental factors as well as by unhealthy lifestyle that includes tobacco use, stress, bad diet, obesity and alcohol use. The aforementioned factors are believed to be involved in the development of 90% of all cancer types.[64] Therefore, it seems that the odds of developing cancer are significantly affected by our lifestyle choices. Several uncontrollable risk factors are involved in the majority of cancer types; however we can change our daily habits in order to reduce this threat.

The use of opioids analgesics for pain management in cancer patients constitutes an appropriate therapeutic option when medical reasons dictate it, such as in acute pain. Providing information to the patients and their relatives regarding the treatment plan contributes to a higher level of compliance and reduces the risk of abusing these drugs.

Tobacco and alcohol abuse in cancer patients aggravates the prognosis of cancer and acts as a negative factor for the quality of life of these patients. These data highlight the need for the development and implementation of appropriate interventions regarding these patients.

Εξαρτήσεις και καρκίνος

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Η χρήση των εξαρτησιογόνων ουσιών αποτελεί, μεταξύ πολλών άλλων, ένα υγειονομικό πρόβλημα με σοβαρές ψυχολογικές και ψυχιατρικές διαστάσεις, ενώ συνοδεύεται από δυσμενέστατες κοινωνικές και οικονομικές επιπτώσεις. Παράλληλα, ο καρκίνος είναι μία νόσος απειλητική όχι μόνο για τη ζωή και τη σωματική ακεραιότητα, αλλά και για την ψυχική υγεία. Οι ογκολογικοί ασθενείς εμφανίζουν ψυχικές διαταραχές σε υψηλά ποσοστά, με προεξάρχουσα την κατάθλιψη και τις αγχώδεις διαταραχές. Ο ρόλος των εξαρτησιογόνων ουσιών στην αιτιοπαθογένεια του καρκίνου μελετάται συστηματικά, αφού υπάρχουν ερευνητικά δεδομένα που υποστηρίζουν τη μεταλλαξιογόνο δράση ορισμένων από αυτές. Η διαταραχή της λειτουργίας του ανοσοποιητικού συστήματος, που πιθανόν προκαλούν ορισμένες από τις ουσίες αυτές, φαίνεται να σχετίζεται με την ογκογενετική τους δράση. Ειδικότερα, τα οπιούχα είναι οι πρώτες εξαρτησιογόνες ουσίες που ταυτοποιήθηκαν ως παράγοντες ογκογένεσης. Ωστόσο, από μελέτες πειραματοζώων έχουν υποστηριχθεί αντικρουόμενα αποτελέσματα· για παράδειγμα παρατηρήθηκε όχι μόνον ενίσχυση αλλά και αναστολή της διαδικασίας της αύξησης των όγκων, ανάλογα με τη δόση του χορηγούμενου οπιοειδούς, όπως της μορφίνης. Επιπροσθέτως, υπάρχουν ερευνητικά δεδομένα τα οποία δείχνουν ότι η χρήση της ινδικής κάνναβης μπορεί να σχετίζεται με τον καρκίνο είτε ως αυτόνομος παράγοντας είτε σε σχέση με άλλα μεταλλαξιογόνα, όμως δεν είναι ακόμη σαφές σε ποιον βαθμό αυτές οι δράσεις της ουσίας μπορεί να συνδέονται με τη νόσο, ειδικά αφού συνυπολογισθούν η κατανάλωση καπνού και αλκοόλ στους συγκεκριμένους ασθενείς. Παρόλ' αυτά έχει υποστηριχθεί ότι ορισμένα κανναβινοειδή πιθανόν να έχουν βιολογικές δράσεις που μπορούν να αξιοποιηθούν θεραπευτικά, όπως είναι οι αντικαρκινικές, χωρίς να συνοδεύονται παράλληλα από την αντίστοιχη ψυχοδραστική επίδραση της 9-τετραϋδροκανναβινόλης. Είναι γνωστό εδώ και πολλά χρόνια ότι το αλκοόλ αποτελεί παράγοντα κινδύνου για την ανάπτυξη καρκίνου στην κεφαλή και στον τράχηλο, ενώ επιδημιολογικές μελέτες δείχνουν ότι όσο μεγαλύτερη είναι η κατανάλωση του αλκοόλ, τόσο αυξάνει η θνησιμότητα από καρκίνο, και επιπλέον ότι δεν υπάρχει επίπεδο ασφαλείας στην κατανάλωση του αλκοόλ σε σχέση με τον κίνδυνο ανάπτυξης καρκίνου, δηλαδή έστω και η ελάχιστη ημερήσια κατα-

νάλωση συνδέεται με την εμφάνιση ορισμένων μορφών της νόσου. Στον καπνό έχουν αναγνωριστεί συγκεκριμένα συστατικά που θεωρούνται καρκινογόνα και υπεύθυνα για την ανάπτυξη της νόσου με διάφορες εντοπίσεις. Επίσης, επιπλεγμένα ψυχιατρικά προβλήματα προκύπτουν από την κατάχρηση των ουσιών στους ογκολογικούς ασθενείς, είτε στα πλαίσια της αντιμετώπισης του πόνου είτε στα πλαίσια προϋπάρχοντος ψυχιατρικού ιστορικού εξάρτησης. Η λελογισμένη αξιοποίηση των οπιοειδών αναλγητικών, με διαφορετική προσέγγιση όπως προτείνεται από τους ειδικούς στην αντιμετώπιση του οξέος πόνου από τον χρόνιο πόνο των ογκολογικών ασθενών, υπαγορεύει μία προσεκτική μεν, αλλά και χωρίς δισταγμούς χρήση τους εφόσον αυτή απαιτείται ιατρικά. Παράλληλα, η κατάχρηση ουσιών όχι μόνο δυσχεραίνει τη συμμόρφωση στη θεραπεία και επιβαρύνει την πρόγνωση του καρκίνου, αλλά και αποτελεί αρνητικό παράγοντα για την ποιότητα ζωής των εν λόγω ασθενών. Η σύγχρονη σχετική βιβλιογραφία αναδεικνύει τη σημασία των κατάλληλων ψυχιατρικών παρεμβάσεων για την αντιμετώπιση της χρήσης στους ογκολογικούς ασθενείς.

Λέξεις ευρετηρίου: Εξαρτησιογόνες ουσίες, αλκοόλ, κάπνισμα, καρκίνος, ανοσοποιητικό σύστημα, πόνος.

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