

## PREVALENCE AND ETIOLOGY OF THE MOST COMMON MALIGNANT TUMOURS IN DOGS AND CATS

I. TODOROVA

Department of Surgery, Faculty of Veterinary Medicine,  
Trakia University, Stara Zagora, Bulgaria

### Summary

Todorova, I., 2006. Prevalence and etiology of the most common malignant tumours in dogs and cats. *Bulg. J. Vet. Med.*, **9**, No 2, 85–98.

Cancer is a multistage process with a polyfactorial etiology. Its development results from the effect of various carcinogens such as ionized radiation, chemicals and oncogenic viruses. The impact of many endogenous factors – genetic, immune and hormonal, is also very important. Under the effect of these factors, changes in the DNA of genes often occur. Some dogs probably inherit some of abnormal genes that are precondition for the malignant cell transformation. The risk factors influence either directly or indirectly on tumour suppressor genes and oncogenes.

Some DNA (herpes viruses, papova- and adenoviruses) and RNA viruses (retroviruses) are named tumour viruses as they are proved to cause cancer in infected cells. Unlike viral infections that are related only to some of neoplastic diseases, chemical carcinogens play a role in the development of most forms of cancer. Food contains natural chemicals that could also lead to DNA damage and produce cell alterations. The oncogenic effect of ionized radiation, depending on the dose, type of radiation and the way it was released is beyond any doubt too. Hormones are another endogenous factor important for the development of some cancer types, including mammary gland tumours.

The present review summarizes the available literature data about the etiology and risk factors for development of malignant tumours in dogs and cats.

**Key words:** etiology, cat, dog, risk factors, tumours

### INTRODUCTION

The share of malignant neoplasms in small animal pathology (dogs and cats) is incessantly increasing, motivating the studies in the field of tumour pathology aiming to increase the survival time and to improve the quality of cancer patients' life. One of the commonest malignancies in dogs and cats are mammary gland tumours, skin tumours, osteosarcomas and haemopoietic tumours.

Malignant tumours are a pathological hyperbiosis, the etiology and pathogenesis of which are not sufficiently clarified.

Cancer is a disease, which can affect various organs and tissues in the body. There is no single cause or condition that causes cancer. The disease is rather a consequence of many factors, which are active in a certain period of time (Lyman, 1992). The development of cancer is a result of the action of various carcinogens (exogenous factors), such as ionized radiation, chemical agents, and oncogenic viruses. A number of endogenous factors – genetic, immune, and hormonal, are also important. The fact that cancer is more com-

monly observed in older patients, supports the concept that, over the course of time, a combination of factors leads to a normal cell's transformation into a cancer cell. Each of these factors increases the likelihood for the appearance of cancer, and they are therefore called risk factors (Lyman, 1992). The significance of risk factors in the development of cancer is based on their ability to influence the genes inside the cells (Lyman, 1992).

#### PREVALENCE OF MALIGNANT TUMOURS IN DOGS AND CATS

Malignant tumours affect both humans and animals. Cancer is among the leading causes for death among pets (Proschowsky *et al.*, 2003; Bonnett *et al.*, 2005). In a series of more than 2000 autopsies, it was found that 45% of the dogs that lived for 10 or more years, died because of cancer (Bronson, 1982). Dogs are affected by skin cancer 35 times more often than humans are. They are also affected 4 times more often by mammary gland cancer, 8 times more often by bone cancer, and twice more often by leukaemia, than people do (Cullen *et al.*, 2002).

*Mammary gland tumours* are the most frequently encountered group of neoplasms in dogs (Moulton, 1990). They constitute 52% of all neoplasms in female dogs (Brodey *et al.*, 1983). Between 41% (Hahn & Adams, 1997) and 53% (Brodey *et al.*, 1983; Rutterman *et al.*, 2000) of mammary tumours found in dogs are malignant. Male dogs can also be affected by mammary gland cancer, although the cases with them are much less than the cases with female dogs – only 1%, (Rutterman *et al.*, 2000). Mammary cancer is the commonest among dogs between 10 and 11 years of age, with neoplasms rarely seen in dogs less than 4 years of age (Rut-

terman *et al.*, 2000). The occurrences of tumours in cats are half as much as in dogs (MacVean *et al.*, 1978). The frequency of occurrence in cats is 158–470 / 100,000 animals, while for dogs it is 381–1126 / 100,000 (Cullen *et al.*, 2002). Around 35–45% of all tumors in cats are of the type that affects the skin and the soft tissues, while haemopoietic malignancies constitute 30–40% of the whole (Hardy, 1981). Mammary gland tumours in cats are third in prevalence, after haemopoietic and skin tumours (Misdorp *et al.*, 1999; Moulton, 1990). Approximately 86% of all feline mammary gland tumours are malignant (Carpenter *et al.*, 1987; Hahn & Adams, 1997). With the exception of mammary tumors, which are more often encountered in sexually intact females than in males and spayed females, no relation between gender and the appearance of tumours in cats could be found (Gabor *et al.*, 2000). The average age of peak prevalence of tumours in cats is approximately 9.3 years (Roccabianca *et al.*, 2006; Tomek *et al.*, 2006). Mammary tumours can also affect male cats, with the average age for them being 12.8 years (Skorupski *et al.*, 2005). Breed predisposition has been found in Siamese and Oriental cat breeds, which fall under greater risk (Louwerens *et al.*, 2005; Gabor *et al.*, 2001).

Second in prevalence are *skin tumours*. They make up 30% of neoplasms in dogs (Priester, 1973). In dogs, these specific tumours have a share of 15–20% of the total (Carpenter *et al.*, 1987). Around 55% of skin tumors in dogs originate from the mesenchymal tissues, the other 45% – from the epithelium (Priester, 1973). The commonest of the mesenchymal tumors in dogs are the histiocytomas, lipomas, fat tissue cells tumors, and the fibrosarcomas (Carpenter *et al.*, 1987;

Miller *et al.*, 1991). In Siamese cats, fat tissue tumors are encountered three times as much as in other feline breeds (Miller *et al.*, 1991). Of the epithelial skin tumors in dogs, the most prevalent are tumours in the fat tissue cells and papillomas, while in cats, the most prevalent are basal cell tumours, and squamous cell carcinomas (Carpenter *et al.*, 1987; Miller *et al.*, 1991).

*Osteosarcomas* are another frequently encountered malignancy in dogs, diagnosed in 50–90% of all primary bone tumors (Cooley & Waters, 1997; Jongeward, 1985). They show a tendency for occurrence in giant dog breeds, and at a younger age, in comparison with small dog breeds of weight under 15 kg, where only adult animals are affected (Chun & Lorimier, 2003). The highest frequency of development of osteosarcoma is observed in large dog breeds, at the age of 7 years (Heyman *et al.*, 1992), while in small breeds, that age is 10.5 years (Cooley & Waters, 1997).

One of the commonest *haemopoietic tumours* in dogs and cats is lymphoma (Ettinger, 2003). The incidence of malignant lymphoma in cats is 6 times higher than in dogs (Schneider, 1983). According to Schneider (1983) the spaying of female cats reduces the risk of development of this tumour type by 50%, but doesn't have a similar effect in bitches.

In our country, retrospective studies of tumour epidemiology in dogs reveal that mammary tumours are prevalent, and that Bolognese dogs, above eight years of age are the most affected, with over 60% malignancy (Dinev *et al.*, 2002). The epidemiology of tumours in cats has not yet been studied in our country.

These statistical data provide a rationale for more research to be performed in the field of tumour pathology, with the

aim of increasing the time of survival and quality of life of patients affected by malignant neoplasms.

## ETIOLOGY AND RISK FACTORS

### *Gene mutations as a commencement of carcinogenesis*

At cellular level, the cancer is characterized with uncontrolled cell growth. Cancer cells undergo a process of transformation from normal to malignant phenotype, with ability for autonomous growth (Loeb & Loeb, 2000). A number of theories attempt to explain malignant transformations of normal cells:

- Mutations can change the genetic nature of somatic cells, through which cell death and proliferation are controlled (Jefford & Irminger-Finger, 2006).
- Atypical differentiation of normal cells is a result of the action of agents, which lead to changes in cell differentiation and to destruction of cellular regulatory mechanisms (Zavadiil *et al.*, 2004).
- Normal cell genes, called protooncogenes, acquire the ability to induce neoplastic transformation (Spandidos, 1985).

Genes are responsible for the control of normal functions within cells. Often changes in the deoxyribonucleic acid (DNA) building those genes occur (Loeb & Loeb, 2000). These changes (genetic mutations) can carry into effect cellular processes. The changes in the DNA information could be accidental, as a result of infectious agents, or a consequence of other agents, causing damage to DNA (Loeb & Loeb, 2000). In many cases, cells are capable of locating and repairing mutations before the cell is damaged. For

instance, the so-called tumour-suppressor genes code special cell proteins that stop cell replication if its DNA is damaged (Ghosh & Bose, 2005). When this system of defense is functioning, a cell with DNA mutation could not transmit the defective genetic material to daughter cells. In a case of low-degree damage, the cell continues its growth cycle after the damage is being removed. If the damage is too extensive, then a process known as programmed cell death (apoptosis) is triggered that results in self-destruction of the cell (Steller, 1995; Ghosh & Bose, 2005). In a case where tumor-suppressing genes (coding proteins that inhibit the synthesis of DNA, the cell growth and division) undergo a mutation, the cell growth could be unlimited (Ghosh & Bose, 2005). Such a tumor-suppressor gene is p53 that plays an important role in carcinogenesis via regulation of cell proliferation, genome stability, and programmed cell death (Hainaut *et al.*, 1997). The cells inherit two copies of each tumour suppressor (Ghosh & Bose, 2005). According to the authors, the mutation of just one copy of the p53 tumor-suppressing gene is needed to result in the development of cancer.

According to Wakui *et al.* (2001) the mutations of the tumour-suppressor gene p53 are related to the development of breast cancer in humans and canine mammary tumours. In a study of dogs with various tumour types, inactivation of the tumour-suppressor gene p53 was established (Setoguchi *et al.*, 2001). In men with breast cancer with evidenced alterations of the p53 gene, the prognosis is poor. The studies of Lee *et al.* (2004) and Haga *et al.* (2001) showed that in dogs, the p53 gene mutation is a sign of increased malignant potential and a bad prognostic sign for mammary gland tumors. About 17 % of mammary gland

carcinomas in dogs showed a p53 gene mutation. A long-term analysis has shown that p53 gene mutations are independent risk factors for the higher risk of recurrence of mammary carcinoma (Wakui *et al.*, 2001).

Other significant genes are the protooncogenes, which enhance DNA synthesis, cell growth and division. These genes are necessary during the individual's development, and, afterwards, to support the new growth of cells that replace the old or damaged cells. If these genes are activated in the conditions of a mutation, they are transformed into oncogenes, and they would make cells grow and divide infinitely (Spandidos, 1985). Such oncogene is p185, which was found in canine malignant mammary gland tumors, and is considered as a poor prognostic sign (Schafer *et al.*, 1998).

It has been determined that a breed predisposition towards malignant growth does exist (Priester & McKay, 1980; Cullen *et al.*, 2002). Dog breeds with a high rate of affected animals are Boxers, Golden Retrievers, Rottweilers, Boston Terriers, English Bulldogs, Cocker Spaniels, while breeds that exhibit a low incidence of disease are Beagles, Collies, Great Danes (Priester & McKay, 1980; Cullen *et al.*, 2002). The breed peculiarities determine the predisposition towards the growth of different kinds of tumours. Breeds such as Poodle, English Spaniel, English Setter, and Terriers, exhibit a higher risk of mammary gland tumors, while for other breeds, such as Boxer and Chihuahua, that risk is minimal (Rodney & Page, 2001; Cohen *et al.*, 1974). In a similar fashion, giant breeds such as Saint Bernard, and Great Dane are affected much more frequently by osteosarcomas, in comparison with dogs of smaller sizes (Chun & de Lorimier, 2003). Cats and

dogs with white skin and hair develop skin carcinomas under the influence of ultra-violet rays. Black and dark-pigmented animals suffer more from melanomas (Rosenthal, 1998). The reason for this natural predisposition is not known, however some dogs do inherit abnormal genes (oncogenes), selected together with the sought genetic traits coding the morphological features of the breed (Sorenmo, 2003).

As a conclusion, the inactivation of tumor-suppressor genes or the activation of oncogenes, the changes within other genes demanding the correction of damaged DNA, or apoptosis are among the prime causes for normal cells to transform into cancer cells (Spandidos, 1985; Anderson *et al.*, 1992; Hainaut *et al.*, 1997).

#### *Exogenous carcinogens*

These are environmental factors – exogenous carcinogens – viral agents, chemicals, and physical factors.

*Tumour viruses.* Some DNA viruses (herpes-, papova-, and adenoviruses) and RNA (ribonucleic acid) viruses (retro viruses) are known as tumour viruses, since they are proved to be causing cancer in cells they have infected (Bishop, 1980; Madewell & Theilen, 1987). It was found that DNA viruses more frequently determine the development of benign tumors in dogs and cats – fibromas, papillomas, and other, while RNA viruses induce malignant tumors (Gabor *et al.*, 2001; Louwerens *et al.*, 2005; Terai & Burk, 2002). Such tumour viruses were found in skin cancer (Allison, 1965; Sourvinos *et al.*, 2000; Terai & Burk, 2002), leukaemia, and mammary gland tumours (Sourvinos *et al.*, 2000). They initiate tumours by integrating their own genetic material inside, or close to the location of the pro-

tooncogenes in the DNA of infected cells (Sourvinos *et al.*, 2000). This integration of alien DNA may change the protooncogenic DNA. When this happens, protooncogenes are transformed into oncogenes (Sourvinos *et al.*, 2000). The protein coded by the action of the protooncogenes is also structurally and functionally changed, and could lead to a normal cell's transformation into a cancer cell (Sourvinos *et al.*, 2000).

It was determined that the most frequently encountered neoplasm of the haemopoietic system in cats, the lymphoma, is related to a retroviral infection (FeLV) (Louwerens *et al.*, 2005).

*Chemical carcinogens.* Unlike viral infections, which can only be related with several specific cancer diseases, chemical carcinogens are involved in the development of most cancer conditions (Loeb & Loeb, 2000). There are two groups of chemical carcinogens – direct and indirect (procarcinogens). Indirectly acting carcinogens, contrasting to former ones, require a metabolic activation by enzymes normally present in the body, in order to become carcinogenic (Wild & Kleihues, 1996). Indirect activation usually occurs during normal physiological processes, when the body eliminates toxic substances in the bloodstream. Many toxic substances, to which the body is exposed daily, are insoluble, which requires that the liver, one of the most important organs responsible for the filtration of blood, to convert the insoluble substances through enzyme reactions into soluble, so that they can be eliminated by the body. Some toxic substances require a longer reaction time in order to be turned into soluble metabolites. If these metabolites are highly reactive molecules, they can alter cell DNA before being removed from the body.

The following substances have a relation with carcinogenesis (Palmer & Mathews, 1986):

- *Nitrates and nitrites.* They are contained in many foods and in the organism could be transformed into N-nitroso compounds, most of which are carcinogens for many laboratory animal species. Epidemiological studies show that those compounds can be carcinogens for humans as well. Acrylonitriles and polyvinylchloride, used as packing material for food have a strong carcinogenic effect on rodents.
- *Polycyclic aromatic hydrocarbons.* These are compounds produced during smoking and food baking, and they have carcinogenic effects on laboratory animals.
- *Polychlorinated biphenyls:* They are found in fish and meat, and are carcinogenic for rodents, producing liver tumors.

According to Ames *et al.* (1990) natural chemicals are found in food, which can lead to damages in DNA and induce cell alterations. The intake of such natural DNA-damaging chemicals with food is much greater than that due to exposing the body to chemicals originating from industry (Ames *et al.*, 1990).

It has been determined that the exposure of dogs to herbicides used in gardening is a risk factor for the development of urinary bladder carcinomas (Glickman *et al.*, 2004). In dogs living in industrial areas, the age boundary of the commonest tumour diseases is significantly lowered (average  $6.1 \pm 0.4$  years) (Gavazza *et al.*, 2001).

*Physical carcinogens.* This group includes radiation, foreign bodies, and hyperthermia. There are two types of radiation, which have significance in the etiology of cancer – ultraviolet and ionized

radiation (Upton, 1978). Subcategories of ionized radiation are electromagnetic radiation, as well as X-rays and  $\gamma$ -rays, and corpuscular radiation, which includes electrons, protons, neutrons,  $\alpha$ -particles, heavy ions. Ionized and ultraviolet radiation alter DNA, interacting with its cellular replication and suppressing its information, coding cellular proteins (Lyman, 1992). A typical event for ionized radiation is the emission of enough energy to break the chemical bonds (Vasilenko *et al.*, 1986). Ionized radiation (atomic particles and X-rays) cause cleavage of DNA bonds, while ultraviolet radiation causes chemical changes in amino acids, which build up DNA (Guzman, 2003). The nature of the damage caused by ionized radiation is such that it is very hard to be corrected by cell mechanisms because during correction, the segment of broken DNA can attach itself to another broken segment, and disrupt the sequence of basic base ordering.

The oncogenic effect of ionized radiation depends on the individual dose, the type of radiation, and the way it was released (Lyman, 1992). It is considered that X-rays and  $\gamma$ -rays are the cause for the production of highly reactive molecules, such as free radicals. The released energy causes an electron to be moved from  $O_2$  and the formation of the free superoxide anion radical ( $\cdot O_2^-$ ), which can cause damage of DNA (Biaglow, 1981). Free radicals are formed in the body as a product of natural biological processes within it, but are immediately neutralized by the natural antioxidant protection mechanisms. In the cases when the balance between produced free radicals and active antioxidants is impaired, oxidative stress occurs. The increased level of free radicals in the body or a lowered antioxidant protection can cause DNA damage and

direct inhibition of proteins (Chopra & Wallace, 1998). One of the most reactive free radicals – the hydroxyl radical ( $\cdot\text{OH}$ ) can capture electrons from tyols, thus interacting with the nitrogen bases of nucleic acids and changing the genetic information of the cell, i.e. it possesses a potential for tumour genesis (Castillo *et al.*, 2002).

Several studies have shown that there are more cases of chronic leukaemia, thyroid tumours, breast cancer in humans exposed to radiation and increased incidence of lung cancer after exposure to radioactive ore (a typical condition for miners) (Kohn & Fry., 1984). In dogs, radiation-induced tumours appear in 30 to 78 months after radiation therapy (Thrall *et al.*, 1981; Thrall *et al.*, 1983). Such cases are very rare and they should not be a cause to refuse radiotherapy. In dogs and cats, ultraviolet sun radiation can lead to the appearance of squamous cell carcinomas (Dorn *et al.*, 1971; Madewell *et al.*, 1981). It has been proved that ultraviolet radiation is a strong carcinogen for the occurrence of skin cancer in dogs, acting simultaneously as an inducer and promoter (Guzman *et al.*, 2003).

#### *Endogenous factors*

To this group, genetic, immune and hormonal factors are belonging.

*Inherited genetic defects.* Usually, cancer diseases caused by external carcinogens appear in older patients, while cases caused by inherited genetic defects occur in younger patients. During a study on two families of dogs, with strongly differing phenotypes, one of which with known predisposition, the other exhibiting resistance towards tumour development, it was determined that the average age of tumour incidence of the first family was significantly lower than in the other one

(Schafer *et al.*, 1998). The inherited genetic anomalies reduce the latent period because the body already has internal vulnerability alterations and a single external influence could be sufficient for the transformation of normal cells into cancer cells.

Inherited genetic defects usually appear as foetal mutations, when genes controlling tumor suppression are inactive, or oncogenes in the semen or the ovum of the parents are active.

Little is known about the inheritance factors of tumour development in dogs and cats. Studies in this field are controversial. Inherited mutations of BRCA 1 and BRCA 2 genes were found in studies on dogs affected by mammary gland cancer (Schafer *et al.*, 1998). At the same time, research by Lloyd *et al.* (2005) showed no clear data on the genetic inheritance of canine mammary cancer.

*Immune system.* It is believed that the immune system can also be involved in the identification and elimination of cells, which undergo transformation from normal into cancer cells – a process known as immune surveillance. For example, many of the very young or very old animals have reduced immune responses and exhibit higher vulnerability towards the action of carcinogens. Animals, whose immune systems are deliberately suppressed, exhibit higher probability to be affected by cancer when exposed to carcinogens, in comparison with non-suppressed animals, whose immune systems were stimulated. For example, dogs with innate immune deficiencies suffer a 2–4% higher frequency of cancer (Rosenthal, 1998). The cellular immune response is mainly involved in the process, and the role of the humoral immunity is not yet clear (Rosenthal, 1998). The primary immunological factor, which has a relation to-

wards the spread of tumors is the activity of the natural killer cells (NK cells) (Ben-Eliyahu & Page, 1992). Acute pain suppresses the cytotoxicity of the NK cells, and promotes tumour development in animals (Page *et al.*, 2001).

*Hormonal factors.* Hormones are another endogenous factor playing an important role in the development of various neoplastic types, including mammary tumours. In young animals, due to the activity of hormones, cells could divide, thus the organs and the organism as a whole grow and develop. In adult animals, hormones control the cell growth in various aspects of the reproductive cycle in both male and females. In the presence of activated oncogenes or inactivated tumour-suppressor genes into the cells, hormones are factors that would stimulate abnormal cells to divide and to become tumorigenic. That is why, it is supposed that the excessive stimulation of some organs by hormones increased the probability of development of neoplasms in them (Rodney & Page, 2001).

Canine mammary tumours are hormonally dependent. Various studies upon the hormonal effects in tumour genesis showed that between 50% and 60% of all malignant mammary tumours in bitches contain estrogen receptors (ER) (Sobczak-Filipiak & Malicka, 2002), more than 30% – progesterone receptors (PR) and more than 20% – androgen receptors. Also, these receptors were present in about 70% of benign mammary tumours (MacEwen *et al.*, 1982; Martin *et al.*, 1984; Donnay *et al.*, 1993). According to other studies, only malignant tumours hold ER (Gerald *et al.*, 2000). In cats, mammary tumours are also common, but the role of hormones in their development is not quite clear. Unlike dogs, the level of ER in feline malignant mammary tumours was

not high whereas the level of PR in these tissues was significant (Martin de las Mulas *et al.*, 2002). The cause and the significance of this fact are not known, but it could influence the choice of therapy. In cats treated with gestagens for oestrus control, the development of mammary cancer is much more likely to occur (Rodney & Page, 2001).

The treatment of dogs with some hormonal drugs as oestrogens and gestagens could also increase the risk of mammary tumours appearance. Oestrogens and progesterone are hormones with a strong stimulatory effect in canine mammary cancer (Key & Pike, 1982). The risk for development of mammary neoplasms in bitches is 0.05% if they are spayed prior to their first estrus (about the age of 6 months), 8% – if spayed after the first oestrus and 26% after the second one (Schneider *et al.*, 1969). The incidence of mammary tumours in intact bitches is seven times higher compared to dogs spayed at the age of 2 years or earlier (Dorn, 1968; Sorenmo, 2003). The early castration could reduce the number of malignant incidents, because the source of hormones is surgically removed. The hormones are causing some mammary cells to lose their controlled growth exposing them to increased risk of mutation and malignant transformation under the carcinogenic environmental influence (Sorenmo *et al.*, 2000).

The timing of ovariectomy is also important for the time of survival in dogs (Sorenmo *et al.*, 2000). The exposure to estrogens or the use of hormonal combinations in the first few years probably initiates the tumour development, the neoplasms being not clinically manifested for years (Lemon, 1977).

Sexually intact cats are also at a higher risk for mammary tumour development vs

spayed cats (Overley *et al.*, 2005). In cats spayed before the age of 6 months, the risk of mammary tumour development was reduced by 91%, and in those spayed prior to the age of 1 year – by 86% (Overley *et al.*, 2005).

Hormones are obviously causing neoplasms both directly as well as together with carcinogens. Oestrogens could be covalently bound to DNA. Diethylstilbestrol could induce a mutation and neoplastic transformation in tissue cultures (Jaggi *et al.*, 1978).

## CONCLUSION

The reviews of scientific reports on the subject revealed significant recent advances. They support the view that the appearance and development of the cancer is a multi-stage process, with numerous etiological factors that are mutually related. The regulation of cell proliferation, genome stability and programmed cell death are important for systemic homeostasis. This equilibrium in the organism is maintained primarily by two types of genes: the so-called tumour-suppressor genes that code proteins, inhibiting DNA synthesis, the cell growth and division, and protooncogenes, that enhance DNA synthesis, cell growth and division. It is hypothesized that the inactivation of tumour suppressor genes or the activation of oncogenes, the alterations in other genes requiring repair of damaged DNA or apoptosis are among the primary causes for the transformation of cells from normal to neoplastic state. The risk factors (exogenous and endogenous) that enhance the susceptibility of individuals to tumour development, influence directly or indirectly upon tumor suppressor genes and oncogenes.

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Paper received 07.06.2005; accepted for publication 02.05.2006

**Correspondence:**

Irina Todorova  
Department of Veterinary Surgery,  
Faculty of Veterinary Medicine,  
Trakia University,  
6000 Stara Zagora, Bulgaria  
e-mail: itodorova@uni-sz.bg;  
irkatodorova@abv.bg