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Neoplastic Disorders in Nonhuman Primates

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Table of Contents

Abstract **3**

Introduction **4**

Discussion **5**

1.0 Etiologic and Hereditary factors that influence neoplasia 5

1.1 Age and Neoplasia 5

1.2 Hereditary Aspects of Cancer in Nonhuman Primates 6

1.3 Chemical Carcinogenesis 6

1.4 Radiation Carcinogenesis 9

1.5 Viral Carcinogenesis 10

2.0 System Specific Neoplasia **13**

2.1 Neoplasia of the Digestive System 13

2.2 Neoplasia of the Urogenital tract 15

2.3 Neoplsais of the Endocrine System 16

2.4 Neoplasia of the Integument and Breast 16

2.5 Neoplasia of the Musculoskeletal System and Connective Tissue 17

2.6 Neoplasia of the cardiovascular and Pulmonary System 18

2.7 Neoplasia of the Hematopoietic System 18

2.8 Neoplasia of the Central and Peripheral Nervous System 19

3.0 Treatments and Prognosis **20**

Conclusion **24**

Bibliography **25**

Abstract

The occurrence of neoplasia in nonhuman primates is a relatively new area of study, hindered by a lack of research and data. However, the similarities between nonhuman primates and humans provide a foundation for understanding the factors that contribute to tumorigenesis in these animals. Despite the limited knowledge, several contributing factors have been identified in various species, including genetic predispositions, ionizing radiation, chemical carcinogens, and viruses. The frequency of reported neoplasms varies across different organ systems, with some showing a higher likelihood of tumor development. While this variation may be attributed to underreporting of certain neoplasms, it is also possible that there are genuine differences in tumor incidence between species. Despite the striking similarities between human and nonhuman primate neoplasms, a notable knowledge gap persists in the clinical management of spontaneous and experimentally induced neoplasms in nonhuman primates. This knowledge gap is particularly concerning given the close similarities between human and nonhuman primate neoplasms. However, a logical conclusion can be drawn that diagnostic and therapeutic approaches developed for humans and domestic animals can be adapted for use in nonhuman primates. The study of neoplasia in nonhuman primates provides a unique opportunity to gain insights into the mechanisms of tumorigenesis and to compare these with human cancer development. In addition, the observation of neoplasms in nonhuman primates can expand the understanding of the impact of environmental and lifestyle factors on cancer risk. Overall, while more research is needed to fully understand the occurrence and causes of neoplasia in nonhuman primates, the existing evidence provides valuable insights into the complex interplay of factors that contribute to tumorigenesis in these animals. By studying neoplasia in nonhuman primates, it provides at the same time a better understanding of the biology of cancer and potentially identify new targets for cancer prevention and treatment. Several articles and methods were evaluated, and the literature reviewed.

Introduction

The development of cancer is a complex phenomenon that arises from the intricate interplay of multiple factors (Causes. Stanford Health Care et al., 2017). In man, rather than a single cause, it is believed that a combination of genetic, environmental, and constitutional factors converge to contribute to the onset of the disease (Causes. Stanford Health Care et al., 2017). Although the etiology of neoplasms in nonhuman primates is largely unknown, several contributory causes have been identified in different species; including genetic factors, ionizing radiation, chemical carcinogens, and viruses (Weller et al., 1998). For example, the effect N-Methyl-N-nitrosourea (MNU) exerts direct carcinogenic effects and does not require enzymatic activation (Takayama et al., 2008). It was also found to be the only carcinogen to consistently produce neoplasms in the digestive tract of non-human primates, particularly squamous cell carcinoma of the esophagus (Miller et al, 2012).

Although neoplasia was once considered to be unheard of in nonhuman primates, it is now increasingly common as nonhuman primates colony populations age (Brown et al., 2009). This trend can also be seen in captive populations of primates since the average age of the populations has increased steadily. There has been an increase in the number of reported tumors in nonhuman primates (DePaoli et al., 1982). This correlation of age with neoplasia has long been recognized in other species, including man (DePaoli et al., 1982). The association of cancer with advancing age in the nonhuman primate is evident particularly with malignant neoplasms of the gastrointestinal tract (DePaoli et al., 1982), particularly in adenocarcinoma of the large intestine (Simmon et al., 2011).

With regards to the clinical management of spontaneous or clinically induced neoplasms in nonhuman primates, given the similarity to those found in human subjects, it is reasonable to assume that the methods for diagnosing and treating neoplasia in humans can be directly applicable to treating neoplasia in nonhuman primates (Miller et al., 2012). One method in preventing neoplasia is reducing the risk of exposure to known etiological agents (Miller et al., 2012). However, it is also essential to explore novel and experimental treatments that have shown efficacy in human oncology and may be beneficial for nonhuman primate patients (Miller et al., 2012).

Discussion

1.0 Etiologic and Hereditary factors that Influence Neoplasia

The development of cancer is a complex phenomenon that arises from the intricate interplay of multiple factors (Causes. Stanford Health Care et al., 2017). Rather than a single cause, it is believed that a combination of genetic, environmental, and constitutional factors converge to contribute to the onset of the disease (Causes. Stanford Health Care et al., 2017). These contributing factors can include genetic predispositions, exposure to carcinogens, and individual characteristics that may increase the risk of tumorigenesis (Causes. Stanford Health Care et al., 2017). Although the etiology of neoplasms in nonhuman primates is largely unknown, several contributory causes have been identified in different species; including genetic factors, ionizing radiation, chemical carcinogens, and viruses (Weller et al., 1998).

1.1 Age and Neoplasia

While neoplasia was previously thought to be a rare occurrence in nonhuman primates, it is now increasingly recognized, particularly in aging nonhuman primate populations (Brown et al., 2009). This correlation of age with neoplasia has long been recognized in other species, including man (DePaoli et al., 1982). Particularly in rhesus macaques, they serve as an excellent model species for human aging and disease as they are genetically similar to humans and share many characteristics of aging and age-related diseases (Simmons et al., 2011). In both humans and Rhesus macaques, cancer incidence rises with age, with the highest rates observed in individuals over 60 years old in humans and 20 years old in Rhesus macaque (Simmons et al., 2011). Four of the National Primate Centers, the California National Primate Research Center, the Oregon National Primate Research Center, the Tulane National Primate Research Center, and the Wisconsin National Primate Research Center, maintain colonies of older rhesus macaques specifically set aside for the long-term noninvasive study of aging processes (Simmons et al., 2011). These macaques are housed in indoor research facilities where they are fed controlled diets and are not exposed to many of the known and suspected environmental carcinogens, such as ultraviolet radiation, cigarette smoke, or environmental pollution, therefore serving as excellent comparative oncology models for the investigation of spontaneous neoplasia and age-related disease (Simmons et al., 2011). A survey conducted showed that, incidence of all types of neoplasms increased with age, with the majority of the tumors occurring in animals greater than 20 years old and the most prevalent neoplasm identified was adenocarcinoma of the intestines (Simmons et al., 2011). Previous surveys on spontaneous cancers in rhesus macaques have shown that, unlike in humans, prostate and lung cancer are relatively uncommon in aged nonhuman primates (Simmons et al., 2011). However,

neoplasia affecting the colon is frequently observed, similarly to what is seen in humans (Simmons et al., 2011).

1.2 Hereditary Aspects of Cancer in Nonhuman Primates

Although there is a similarity in genes between non-human primates and humans, humans do have a higher rate of hereditary cancer due to differences in some genes (Memorial Sloan Kettering Cancer Center, 2022). Chimpanzees are humans' closest living relative, sharing about 98.8% of genes, however, in that 1.2 % difference is a change in the BRCA2 gene that causes humans to be more affected by cancer (Memorial Sloan Kettering Cancer Center, 2022). There is a change in an amino acid in the human gene that is not present in the chimpanzee gene, making this gene less functional in humans (Memorial Sloan Kettering Cancer Center, 2022). This is crucial, as BRCA2 gene plays an important role as a tumor suppressor because it is responsible for correcting errors in other genes that can otherwise lead to cancer genes (Memorial Sloan Kettering Cancer Center, 2022). This change was further found to lead to a reduction of 20% in the proteins' ability to repair DNA but still able to boost fertility in humans, therefore making it easier to pass down this mutation in kin (Memorial Sloan Kettering Cancer Center, 2022).

Nevertheless, in nonhuman primates there are still examples of them demonstrating potential hereditary neoplasia, like that of pheochromocytomas in cotton-top tamarins (Saguinus Oedipus) (Miller et al., 2012). Pheochromocytomas are neoplasms of the adrenal medulla, that in man, are associated with familial tumor syndrome because of inherited mutations in proto-oncogenes and tumor suppressor genes (Miller et al., 2009). This study surveyed 114 adult cotton - top tamarins, and thirty-seven of these thirty-seven had malignant neoplasms, from which pheochromocytomas corresponded to 6 (16%) of the total cases (Miller et al., 2009). The animals in this study had a high prevalence of uni- and bilateral pheochromocytomas and a genetic link between affected animals was observed after pedigree analysis was executed, showing that 4/6 or 67% of the affected animals were derived from offspring of one mating (Miller et al., 2009). Colon carcinoma has also been implicated as having a possible hereditary basis in the cotton-top tamarin due to the limited major histocompatibility complex polymorphism in the species. (Miller et al., 2012).

1.3 Chemical Carcinogenesis

Chemical carcinogenesis is a multistep process resulting from exposures, usually to complex chemical mixtures that are often encountered in the environment through lifestyle and diet (Weston et al., 2003), causing an accumulation of genetic and epigenetic changes (Takayama et al., 2008)

because they either change the cells' DNA or may cause cells to divide at faster rate, which increases the chances of DNA changes occurring (American Cancer Society, 2019). However, chemical carcinogenesis in primates is most easily demonstrated in models of experimental carcinogenesis but from these experimental chemical carcinogenesis studies important concepts about the effects of carcinogenic chemicals on the cells have been derived and include the following (Miller et al., 2012):

1. A carcinogenic agent (an initiator) given at a certain dose causes cells to be altered; however, initiation by itself is not enough for a tumor to develop.

2. The initiating event causes permanent damage to DNA that is irreversible.

3. Promoters can cause tumors in cells that have been exposed to the initiator (Miller et al., 2012). Promoters by themselves do not cause tumors as they are insufficient to cause DNA damage directly. Promoters cause proliferation of the initiated cells and allow for a tumor to grow.

In a study carried out by the National cancer institute USA during a 34-year period, they evaluated a total of 37 compounds including 6 antineoplastic agents, 13 food additives, and 5 N-nitroso compounds. Specifically, 166 monkeys were treated with one of the antineoplastic agents and the results showed that the test agents in this category showed evidence of carcinogenicity, with tumor incidences of 6.7-40.9% (Takayama et al., 2008).

Summary of malignant tumor data for monkeys treated with antineoplastic and immunosupressive agents

Agent	No. of monkeys	Route	Daily dose (mg/kg)	No. of dead with malignant tumor	Carcinogenicity
Doxorubicin hydrochloride	10	iv	0.2	0	no
Doxorubicin hydrochloride	10	iv	0.4	1	no
Doxorubicin hydrochloride	10	iv	1.0	1	no
Cyclophosphamide	23	po	6.0	1	not conclusive
Melphalan	20	ng	0.1	2	not conclusive
Procarbazine	49	sc/po, ip/po, or ip	10	17	yes
MNU	43 or 44	po	10	18	yes

Table 1. Summary of malignant tumor data for monkeys treated with antineoplastic and immunosuppressive agents (Takayama et al., 2008).

A total of thirty monkeys received *Doxorubicin hydrochloride (Adriamycin), and two reports of malignant tumors were recorded, which included a case of* acute myeloblastic leukemia in a rhesus monkey and one case of low-grade fibrosarcoma at the injection site in the right leg in a cynomolgus monkey (Takayama et al., 2008). Of the twenty-three monkeys that received

Cyclophosphamide (Cytoxan), one rhesus monkey was found to have a small transitional cell carcinoma of the urinary bladder. Of those treated with *Melphalan (L-PAM),* five cynomolgus monkeys were diagnosed as having malignant tumors at autopsy, one being found to have an endometrial adenocarcinoma, two demonstrating poorly differentiated sarcomas in the perineal and perivaginal area of unknown origin, and one metastasizing to the lung (Takayama et al., 2008). In addition, a prostate carcinoma and a squamous cell carcinoma of the palate were also diagnosed. Apart from the malignant carcinomas found, six animals were also found to have benign tumors (four with leiomyomas of the uterus, one with a lung adenoma, and one with an eccrine cylindroma of the scalp). The animals that were administered procarbazine *(MIH),* seventeen animals *were found with* malignant tumors, and the tumors included 8 cases of acute nonlymphatic leukemia, 2 renal hemangiosarcomas, 3 osteosarcomas, 1 lymphocytic lymphoma, 1 osteocytoma, and 1 colon carcinoma (Takayama et al., 2008). One animal had two primary tumors, in the pancreas and the renal pelvis. N-Methyl-N-nitrosourea (MNU) exerts direct carcinogenic effects and does not require enzymatic activation. Malignant tumors were observed in eighteen animals of which invasive squamous cell carcinomas in the lower third of the esophagus were found in 15 animals; 7 of these animals had a single primary tumor, while the remaining 8 had multiple tumors. In addition, squamous cell carcinomas were found in the oral cavity, pharynx, larynx, and stomach. One cynomolgus monkey had three primary tumors, a squamous cell carcinoma of the esophagus, an adenocarcinoma of the stomach, and a rhabdo-myoblastoma of the heart. All animals with esophageal squamous cell carcinomas displayed severe dysplasia in non-cancerous regions of the esophageal mucosa (Takayama et al., 2008). MNU as a carcinogen was also found to be the only one to consistently produce neoplasms in the digestive tract, particularly squamous cell carcinoma of the esophagus (Miller et al, 2012).

To summarize the study's findings, out of the 401 autopsy reports reviewed, in total their spontaneous tumor findings showed that incidence of total malignant tumors was highest in the African green monkeys (8%), with 3 of 5 malignancies being non-Hodgkin's lymphomas, which is a disease where malignant cells form in the lymphatic system (Takayama et al., 2008). This was followed by rhesus and cynomolgus monkeys with incidences of 1.9% and 3.8%, respectively. The cynomolgus monkeys with tumors had adenocarcinomas of the kidney and colon, and a duct carcinoma of the mammary gland. Seven rhesus monkeys developed malignant tumors, including two rhabdomyosarcomas in their limbs. One of two poorly differentiated sarcomas with unknown primary locations in the peritoneal and perivaginal areas demonstrated metastasis to the lung. The study also included two cases of squamous cell carcinoma, one in the tongue and one in the bladder, in addition to an adenocarcinoma of the bile duct. Spontaneous benign tumors were observed in two

cynomolgus and 11 rhesus monkeys, 6 of the 11 benign tumors in the latter being uterine leiomyomas (Takayama et al., 2008).

1.4 Radiation Carcinogenesis

Radiation carcinogenesis is a biological phenomenon where living cells are damaged by ionizing radiation (Springer et al., 2017). “The universal nature of radiation as a carcinogen relates to a specific characteristic of ionizing radiation that differentiates it from chemical toxic agents or other physical carcinogens, which are usually tissue specific in their action” (Little et al., 2000). This ability to penetrate cells and to deposit energy within them in a random fashion is unaffected by the usual cellular barriers presented to chemical agents. All cells in the body are thus susceptible to damage by ionizing radiation; the amount of damage will be related to the physical parameters that determine the radiation dose received by the particular cells or tissue.

The effects of UV radiation in nonhuman primates are not well known, however, in man, UV radiation is a well-known cause of increased incidence of squamous cell carcinoma, basal cell carcinoma, and malignant melanoma in the skin (Miller et al., 2012). UV light in combination with other carcinogens applied to the skin of rhesus macaques has been linked to the development of skin tumors, like basal cell tumors. Other studies have been conducted using rhesus macaques to determine the effects of whole-body irradiation in order to understand the consequences of total-body irradiation in animal models that closely resemble humans (Sills et al., 2022). In this particular study, 239 rhesus macaques received a single dose of TBI (total body irritation) while the remaining fifty-one served as nonirradiated controls, and the surviving animals were then transferred for long-term monitoring post radiation. This study showed that total body irradiation was associated with an increased incidence of neoplasia, with sixty-one neoplasms (benign or malignant) being diagnosed in 44 out of the 239 animals. Among the forty-four irradiated animals with neoplasms, initial neoplasms were diagnosed 4 months to 14 years after irradiation and 11of the 44 tumor bearing individuals were diagnosed with at least 2 neoplasms. Benign mesenchymal tumors accounted for fourteen out of the 61 total neoplasms and the most common diagnoses were leiomyomas and neurofibromas. As seen in the graph below, neoplasia was detected in most major organs systems, with the most common site being the skin and subcutis.

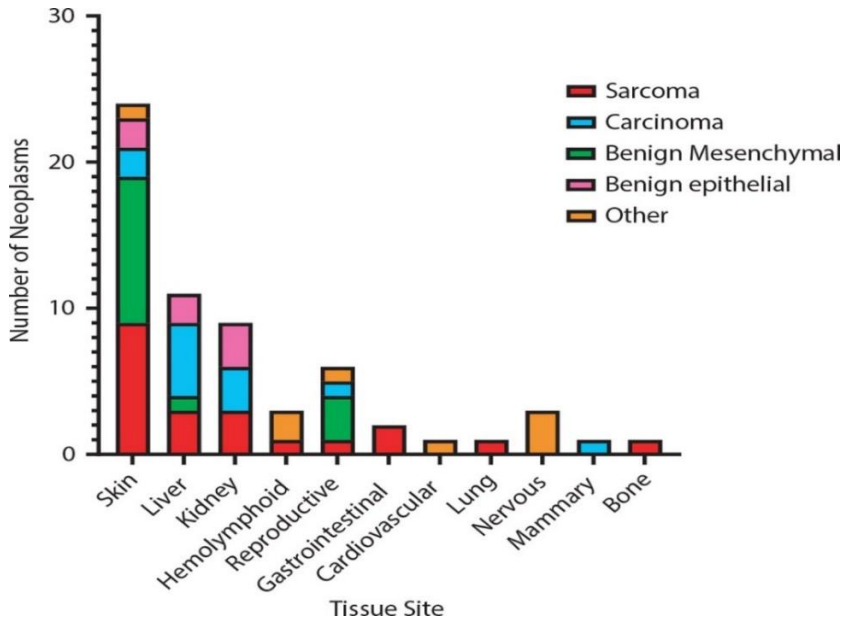

Figure 1. Summary of type of neoplasms and organ system detected in (Sills et al., 2022).

This study further concluded that total-body irradiation is associated with an increased incidence of neoplasia following irradiation, at more than double the incidence described in aging, nonirradiated animals, and promotes tumor histotypes that are rarely observed in nonirradiated, aging rhesus macaques.

1.5 Viral Carcinogenesis

Viral carcinogenesis refers to the process of transformation of normal cells into cancer cells, induced by a virus (Caracciolo et al., 2010). Viruses, when functioning as carcinogenic agents, utilize a variety of carcinogenic mechanisms to transform cells (Chen et al., 2014), like a variety of nonhuman primate viruses can cause malignant cell transformation and neoplasia when introduced in the host adapted species or an aberrant species (Miller et al., 2012). While other nonhuman primate viruses are directly associated with the development of various neoplasms such as rhesus lymphocryptovirus-induced lymphoma, yabapoxvirus-associated subcutaneous histiocytic neoplasms, and papillomavirus-induced cervical papillomas and carcinoma. A brief table of several important oncogenic viruses in nonhuman primates and their mechanisms of oncogenesis is provided below.

Virus	Nonhuman Primate Example	Mechanism od Oncogenesis	Pathology	Species Affected
Rhadinovirus	Herpesvirus saimiri	Oncogene transformation	T-cell lymphoma	Common marmoset, cotton-top tamarin, owl monkey
Lymphocryptovirus	Rhesus lymphocryptovirus	Oncogene transformation; genomic instability	B-cell lymphoma	Rhesus macaque
Rhadinovirus	Retroperitoneal fibromatosis-associated herpesbirus	Unknown	Retroperitoneal fibroproliferative lesions	Rhesus macaque
Deltaretrovirus	Simian T-lymphotropic virus	Oncogene (Tax) Expression	T-cell lymphoma	Baboon
Hepadnavirus	Chimpanzee hepadnavirus	Insertional mutagenesis; chronic inflammation	Unknown	Chimpanzee
Papillomavirus	Cynomolgus papillomavirus	Inactivation of tumor suppressor genes	Papillomas; vaginal and cervical dysplasia and carcinoma	Cynomolgus macaque

Table 2. Summary of several important oncogenic viruses in nonhuman primates and their mechanism of action, pathology and species affected (Miller et al., 2012).

A brief review of selected viral agents is provided below:

Yabapoxvirus

Yabapoxvirus, also known as Yaba Monkey Tumor virus (YMTV), has relatively few documented naturally occurring episodes, owing to the fact that wild-caught animals are resistant (Watchtman et al., 2012). This suggests that widespread infection with YMTV or closely related virus(es) occurs in the wild, conferring life-long immunity to those individuals at an early age while captive-born primates, like captive born African green monkeys, appear susceptible to experimental infection (Watchtman et al., 2012). Yabapoxvirus is mainly associated with subcutaneous neoplasia that is histiocytic in nature (Miller et al., 2012). These tumors develop rapidly but can also be associated with spontaneous regression within 2-3 months. In a study held to understand the pathogenesis of YMTV, where two rhesus monkeys were injected with YMTV, it was discovered that at 48 hours post-inoculation, histiocytes predominated, and these were distributed along the needle tract and deep fascial plane (Sproul et al., 1963). By the third day, the majority of histiocytes in the injection area showed specific alterations, and mitotic activity was evident. On the 4th and 5th days following inoculation of the virus, the proliferating altered histiocytes formed compact 2 to 3 mm. nodules which were usually palpable. By the second week proliferation predominated, and a moderately circumscribed but infiltrative tumor was formed in the dermis and subcutaneous tissues (Sproul et al., 1963). The tumors attained a size of 2-5 cm before regressing and regression appeared to be a simple process of tumor cell disintegration. YMTV can be characterized by multiple subcutaneous masses, often on the hands and feet, varying in size from small papules to nodules several centimeters in diameter (Watchtman et al., 2012). Larger masses also occasionally

ulcerate, and all masses invariably regress by 6 weeks, but ulceration is not a prerequisite for regression (Sproul et al., 1963).

Herpes saimiri and Herpes Ateles

Herpes Saimiri and Herpes Ateles are members of the Gammaherpesviridae subfamily and the genus Rhadinovirus (Watchtman et al., 2012). They are indigenous to squirrel monkeys and spider monkeys, respectively, and do not cause disease in the host of origin, even though infection is common in both wild and captive animals of these species (Miller et al., 2012). Talking specifically about H. saimiri, this is because as natural hosts of HVS, squirrel monkeys are infected via saliva within the first two years of life and HVS does not cause tumors nor disease and establishes lifelong persistence in these species (Fichkenscher et al., 2001). As for H. Ateles, the virus is naturally found in spider monkeys, which does not lead to clinical disease (Mätz-Rensing, et al., 2019) and approximately 50% of spider monkeys are seropositive for AtHV strains (Watchtman et al., 2012). While they typically cause an asymptomatic infection in their natural hosts, inoculation of Yabapoxvirus into other primate species leads to the rapid onset of malignant lymphoma or leukemia. For example, inoculation of H. saimiri into marmosets, spider monkeys, owl monkeys, and cinnamon ringtail monkeys (Cebus albifrons) has been shown to induce a rapidly fatal lymphocytic leukemia and lymphoma (Miller et al., 2012). After inoculation, the development of lymphoma by H. Saimiri can occur within a variable time frame, with some cases manifesting as soon as 3 weeks post-inoculation (Watchtman et al., 2012). The outcome typically follows one of three distinct patterns:

(1) a rapid decline in health, resulting in death within 40 days, often accompanied by widespread lymphoma spread and extensive tissue necrosis;

(2) a more protracted course, characterized by a slower-developing, multi-organ lymphoma and concomitant lymphocytic leukemia, with survival times ranging from 50 to 150 days; or

(3) a slower and more localized growth pattern, with survival times exceeding 150 days and the development of well-differentiated lymphocytic lymphoma.

The outcome of experimental infections with Herpesvirus Saimiri (HVS) largely depends on the specific virus strain (Mätz-Rensing, et al., 2019). Three distinct subtypes of HVS (A, B, and C) can be distinguished based on DNA sequence differences at the left terminus of L-DNA. Subgroups A and C are highly oncogenic, as they have been shown to transform marmoset peripheral blood lymphocytes in vitro and induce rapidly progressing T-cell lymphomas in various New World primate species. Following experimental infection, different disease patterns emerge, depending on the virus strain and host. The time to lymphoma development can range from as short as three weeks to several months, with a mean survival time of 22-42 days. Animals that succumb to the

infection within 40 days typically develop aggressive, disseminated lymphomas characterized by extensive tissue necrosis and replacement, whereas those that survive longer may experience less severe lymphoma development and/or leukemia.

Herpesvirus Ateles has been shown to cause a rapid onset of lymphoblastic lymphoma and acute leukosis in owl monkeys and marmosets following inoculation (Miller et al., 2012). Herpesvirus Ateles has also been shown to cause malignant lymphoma when inoculated into Howler monkeys. While research on Herpesvirus Ateles has been limited, the available evidence suggests that its oncogenic properties are comparable to those of Herpesvirus saimiri (Watchtman et al., 2012).

Both viruses exhibit a rapid capacity to induce polyclonal malignancy, a situation where two or more cells or clones of cells interact to initiate a tumor (Parsons et al., 2008), implying that they possess the complete genetic information necessary for malignant transformation (Miller et al., 2012).

2.0 System Specific Neoplasia

In nonhuman primates, the frequency of reported neoplasms differs across various organ systems (Miller et al., 2012). Spontaneous tumors of the digestive tract are commonly observed in most nonhuman primate species, whereas tumors in other organs, such as the cardiovascular system, are relatively rare. It is likely that some of this variation is attributed to underreporting of certain neoplasms, rather than a genuine difference in tumor incidence. A brief review of the incidence of neoplasia in various organ systems is reported below.

2.1 Neoplasia of Digestive System

Neoplasia of the digestive system is a common occurrence in many nonhuman primate species. In particular, squamous cell carcinomas of the tongue, buccal pouch, and gingiva are the most frequently reported tumors of the oral cavity (Miller et al., 2012). This is observed in various studies, including one where over a 20-year period, 14 spontaneous cases of SCC (13 baboon, 1 spider monkey) in primates were identified at the Southwest National Primate Research Center and 86 additional published cases of spontaneous squamous cell carcinoma were reviewed (Haddad et al., 2009). The results of this study showed that SCC was most commonly reported in macaques, baboons, marmosets, and squirrel monkeys and one of most frequently reported primary locations was the oral cavity, among others. The table below shows the retrospective baboon data for the six cases of SCC in the oral cavity at the Southwest National Primate Research Center.

Tumor Location	Age (yr)	Sex	Tumor Behavior	Presenting Complaint	Treatment Period (from presentation to death)
Oral, Gingiva and mandible	20.2	M	Local invasion of bone	Mandibular cavitation	None; biopsy diagnosis; euthanized
Oral, Gingiva and mandible	26	M	Local invasion of bone	Gingival mass	5 months; biopsy diagnosis; surgical excision attempted; recurrence of tumor; euthanized
Oral, Gingiva and maxilla	3	F	Local invasion of bone and medullary cavity with tumor in blood vessels	Maxillary swelling	3 months; antibiotic therapy unsuccessful; biopsy diagnosis; intralesional chemotherapy attempted; died during treatment
Oral, Buccal mucosa	19.2	F	Local invasion (mucosa and subcutaneous tissue) with extension or metastasis to regional lymph node	Eroded mass on left cheek	None; biopsy diagnosis; lived 3 months post-biopsy to raise young, then euthanized
Oral, Skin and mandible	19.3	F	Local invasion of bone with pathologic fracture	Mandibular fracture	None; euthanized on presentation
Oral, Gingiva, buccal pouch and mandible	20.3	F	Local invasion of bone	Mandibular fracture	None; euthanized on presentation

Table 3. Table summary of squamous cell carcinoma in the oral cavity of six baboons (J. Haddad et al., 2009).

As seen on the table above, of the fourteen spontaneous cases of SCC, 6 (46.2%) of those involved the oral cavity, and of these 6 cases, 5 cases had bone involvement, and one had lymph node involvement. Furthermore, these baboons with SCC presented with irregular soft tissue swelling of the gingiva and buccal mucosa with variable necrosis or ulceration of the oral soft tissues, lose or broken teeth, fracture of the jaw, or abscess formation. Two baboons received treatment for their tumors, while one baboon underwent surgical excision of the tumor, but it recurred within a 5-month period. The second baboon was treated with intralesional chemotherapy, however, the baboon succumbed to the treatment during its course.

As for the literature review done in this study, the most common reported location of SCC in the non-human primates was the oral cavity, with thirty-two cases, not including the 6 baboon cases reported previously. The most frequent nonhuman primate species reported with SCC in the oral cavity in decreasing order were Macaque (12), Baboon (3), Marmoset (6), squirrel monkey (8).

In addition, oral squamous cell carcinoma has been reported in other primate species, including capuchin monkeys, squirrel monkeys, and a cynomolgus macaque (Miller et al., 2012). Ameloblastoma is the most frequently documented tooth tumor in nonhuman primates, with recorded cases in cynomolgus macaques, rhesus macaques, cebus monkeys, spider monkeys, and baboons. Adenocarcinomas of the small bowel and colon have been reported in several species, with the highest incidence of colonic neoplasia being reported in the cotton-top tamarin and the rhesus macaque. The majority of gastrointestinal tumors found in rhesus macaques are ileocecal or

colonic adenocarcinomas, while cotton-top tamarins are most commonly affected by colonic adenocarcinomas. Cecal adenocarcinomas are prevalent in aged baboons, and a similar trend is observed in rhesus macaques, where ileocecal adenocarcinomas are increasingly diagnosed in older populations. Notably, these tumors exhibit many histological similarities to their human counterparts. In rhesus macaques, treatment for ileocecal adenocarcinoma has been attempted in some cases via intestinal resection and anastomosis. In the majority of animals that underwent surgical treatment for ileocecal adenocarcinoma died either due to post-operative complications or the continued progression of the adenocarcinoma. However, there have been occasional cases where surgical intervention appeared to be curative. The histological similarities between colon carcinomas in man and ileocecal adenocarcinomas make this a strong candidate for an animal model to study induction and progression of large intestinal carcinomas. Lastly, in prosimians, especially lemurs, neoplasms of the liver and exocrine pancreas are among the most common malignancies reported but are rare in other primate species. These tumors in prosimians can take the form of hepatocellular adenomas and carcinomas, biliary adenomas and carcinomas, and pancreatic adenomas and adenocarcinomas.

2.2 Neoplasia of the Urogenital tract

Spontaneous tumors of the urinary tract have primarily been reported in the kidney (Miller et al.,2012). In rhesus macaques, renal carcinomas have been reported and have been subcategorized into papillary, tubular, tubulopapillary, tubulosolid, and solid. Renal carcinomas have also been described in cynomolgus macaques, an owl monkey, and a tubulopapillary renal carcinoma has been described in a baboon. Neoplasia is a common occurrence in the female reproductive tract in all species of nonhuman primates. Ovarian tumors in the rhesus macaque are a common occurrence, comprising a diverse range of neoplastic lesions, including cystadenomas/cystadenocarcinomas, choriocarcinoma, placental site trophoblastic tumor, dysgerminoma, teratoma, and granulosa cell tumors . In the rhesus macaque, granulosa cell tumors and teratomas are the most frequently reported types of ovarian tumors. The majority of ovarian neoplasms arise unilaterally; however rare reports exist with tumors arising in both ovaries. Typically, the majority of cases are found as incidental findings during necroscopy, however there are some cases where antemortem hormonal and physical changes suggest an ovarian tumor. For example, increased gonadotropin levels in a rhesus macaque measured in the beginning of a toxicology study was associated with choriocarcinoma (Farman et al., 2005). In monkeys, elevated levels of monkey chorionic gonadotropin (mCG) in the serum or urine typically indicate pregnancy, but in this case, since the monkey was not pregnant (with a histologically normal uterus and no

recent male exposure), the elevated mCG levels were likely produced by the ovarian tumor (Farman et al., 2005). Moreover, in chimpanzees reported ovarian neoplasia includes fibrothecoma, granulosa cell tumor, teratoma, and Sertoli-Leydig cell tumors (Miller et al., 2012). However, new world primates rarely have ovarian pathology with a single case of teratoma reported in a common marmoset. Ovarian neoplasia in prosimians is similarly varied and includes granulosa cell tumor, ovarian carcinoma, and dysgerminoma. Tumors of the male reproductive system have a much lower incidence than tumors of the female reproductive tract, and of the reported male reproductive tumors, testicular neoplasia appears to be the most common . "Seminoma has been reported in an owl monkey, a howler monkey, and an African green monkey". Leydig cell tumors have been described in western lowland gorillas and a unique case of seminal vesicle adenoma has been reported in a cynomolgus macaque.

2.3 Neoplasia of the Endocrine System

For the most part, endocrine tumors in nonhuman primates are generally benign and nonfunctional (Miller et al., 2012). However, in some endocrine organs, like the adrenal gland, tumor incidence tends to be more common in new world species in comparison to old world species. Adrenal gland tumors are typically classified as cortical or medullary, with pheochromocytomas, a type of medullary tumor, being the most commonly reported in new world primates, including golden lion tamarins, cotton-top tamarins and black howler monkey, and mentioned previously, pheochromocytoma has been demonstrated to exhibit potential hereditary basis in cotton-top tamarins. Furthermore, tumors of the thyroid and parathyroid are much more uncommon in comparison to tumors of the adrenal gland. However, nodular thyroid hyperplasia has been reported in both rhesus and cynomolgus macaques and has been described to be functional, therefore being capable of releasing one or more hormones (Vella et al., 2012). In prosimians, particularly Sanford's brown lemur and crowned lemur, thyroid adenomas and cystadenomas have been described (Miller et al., 2012). As for the pituitary gland, tumors of the pituitary gland are most frequently reported in cynomolgus macaques and the majority of pituitary adenomas in this species secrete prolactin. Despite that, rare cases of pituitary adenoma have also been reported in a rhesus macaque, a gorilla, chimpanzees, and a golden lion tamarin. But, once more, the majority of the reported pituitary adenomas have been incidental findings at necropsy.

2.4 Neoplasia of the Integument and Breast

The skin, as the largest organ of the body, protects all other organs systems from various environmental insults, but at the same time, is also exposed to factors that cause disease and cancer

(Miller et al., 2012). Neoplasia of the skin and subcutis are relatively common in nonhuman primates, with the highest incidence being reported in macaques. Although malignant tumors predominate over benign tumors in reports, this is likely due to the fact that benign tumors do go unreported. In man, squamous cell carcinoma is commonly associated with prolonged exposure to UV radiation; however, a similar pathogenesis has not been studied extensively in macaques. The most common malignant neoplasia of the skin is squamous cell carcinoma, being reported to arise spontaneously in various primate species, like rhesus and cynomolgus macaques, baboons, a white-lipped tamarin and a sooty mangaby. In baboons, cases of squamous cell carcinoma are most commonly seen in females around the perineal region, but whether that is related to a specific pathogenesis is unknown. Although rare, benign tumors have been reported, including one case of a benign intradermal junctional melanocytoma in a rhesus macaque and a benign cutaneous mast cell tumors in a rhesus monkey.

In the macaque, the mammary gland is prone to similar neoplasms as those encountered in women and this is partly due to the similarities in development, physiology, menstruation, and reproductive senescence (Miller et al., 2012). In the last decade, neoplasia of the breast of the macaque has become more recognized, including cases in both the rhesus and cynomolgus macaque that range from ductal hyperplasia, atypical ductal hyperplasia, lobular carcinoma in situ, ductal carcinoma in situ, and invasive ductal carcinoma. Like in human breast cancer, some of the higher-grade lesions display increased expression of proliferation markers and HER2 oncogene expression. Clinically, breast cancer in macaques is typically an incidental discovery, but higher-grade lesions frequently exhibit local invasiveness and metastatic potential. In New World primates, there is a lack of documented cases of mammary tumors, leaving it unclear whether this reflects a genuine rarity of the condition.

2.5 Neoplasia of the Musculoskeletal System and Connective Tissue

Tumors of the primary bone, skeletal muscle, and connective tissues are relatively uncommon in nonhuman primates, which may be attributed to the relatively smaller size of most primate species (Miller et al.,2012). Spontaneous bone tumors are most commonly seen in rhesus monkeys, with osteosarcomas typically affecting the skull and appendicular skeleton; however, rare cases of osteosarcoma have also been reported in long bones. In New world monkeys, bony tumors are more uncommon, however, there are several reports of osteosarcoma arising in the long bones of squirrel monkeys and a chondrosarcoma also in a squirrel monkey. In general, in nonhuman primates, neoplasia of skeletal muscle and connective tissue is a rare occurrence; in the rhesus macaque, solitary case reports have described a mixed mesodermal sarcoma, a myxosarcoma, and a

fibrosarcoma. However, in prosimians, the most commonly reported connective tissue neoplasm is a fibrosarcoma.

2.6 Neoplasia of the Cardiovascular and Pulmonary System

In primates, primary cardiovascular neoplasia is extremely rare (Miller et al., 2012). Very few have been reported and described, like a fibrosarcoma arising in the interventricular septum of a middle-aged rhesus macaque and a single case of a spontaneous pericardial mesothelioma, once again, in a rhesus macaque. Neoplasms of the vascular system, on the contrary, are slightly more common and reports include a cavernous lymphangioma in a squirrel monkey, and a cavernous hemangioma affecting the ovary in a rhesus macaque. In comparison to humans, where smoking is the single biggest cause of respiratory tract neoplasia, in nonhuman primates few risk factors have been identified. However, in any case, primary respiratory tract neoplasia is still slightly more common in nonhuman primates than tumors of the cardiovascular system. An extremely aggressive, malignant intranasal carcinosarcoma has even been described in a male bonnet macaque, where the tumor invaded the bony orbit, distorted the position of the globe and even metastasized to the regional lymph nodes and lungs (Slayter et al., 1988). But primary lung cancer in primates is even rarer (Miller et al.,2012). Reports of bronchioloalveolar adenoma has been described in rhesus macaques, where they are uncommon incidental findings encountered in the species.

2.7 Neoplasia of the Hematopoietic System

For decades, malignant lymphoma and leukemia has been described in a variety of nonhuman primates, including rhesus and cynomolgus macaques, African green monkeys, baboons, and common marmosets (Miller et al 2012). However, many of the reports of lymphosarcoma, were made prior to the discovery of oncogenic viruses, therefore the evaluation of the spontaneous nature of the vast majority of lymphoid neoplasms was most likely associated with viral infections. Rhesus lymphocryptovirus, a virus closely related to Epstein-Barr virus (EBV) in humans, has been identified as a common viral cause of lymphosarcoma in macaques. Moreover, this virus-induced cancer is also a common diagnosis in humans in HIV-infected individuals, and a similar scenario exists in cynomolgus, and rhesus macaques infected with simian immunodeficiency virus. Following SIV-mediated immunosuppression, rhesus lymphocryptovirus (LCV) tends to exit latency, triggering the development of peripheral lymphadenopathy in infected animals, which can ultimately lead to the progression to multiorgan lymphoma. Furthermore, a significant number of lymphoma cases have been reported in owl monkeys infected with Herpesvirus saimiri, a gamma herpesvirus that is distinct from the lymphocryptovirus family and belongs to the closely related

rhadinovirus family. While this virus is non-pathogenic in squirrel monkeys, its transmission to owl monkeys, tamarins, and marmosets is associated with the development of lymphoproliferative diseases and lymphoma. Similarly, the presence of ateline herpesvirus is enzootic in spider monkey populations, where it is non-pathogenic. However, when this virus is inoculated into owl and squirrel monkeys, it induces identical lymphoproliferative diseases to those caused by Herpesvirus saimiri. While many lymphomas in New World primates are linked to viral infections, there are some exceptions, as scattered cases of spontaneous lymphoma have been observed in cotton-top tamarins.

Moreover, neoplastic lesions similar to those that manifest in humans have also been reported, for example a lesion similar to a human littoral cell angioma has been reported in the spleen of an aged Japanese macaque (Miller et al., 2012). The 30-year-old Japanese macaque developed weight loss and anorexia and upon necroscopy presented an enlarged spleen, of which the pathologic characteristics bore a resemblance to those of littoral cell angiomas of the spleen in humans (Yamate et al., 2009). However, in humans, splenic vasoformative disorders are often accompanied by a disturbance of blood coagulation (Yamate et al., 2009). Therefore, thrombotic, and antithrombotic factors, as well as neovascularization factors were also further investigated. Upon further investigation, gene expression analysis revealed that tissue factor was upregulated, whereas plasminogen activator inhibitor-1 was suppressed. Notably, in antithrombotic factors, tissue factor pathway inhibitor mRNA levels were increased, but that of thrombomodulin did not change. While the gene expressions of tissue factor and associated proteins were elevated in the affected spleen, the blood levels of these proteins were within normal range, suggesting that the blood coagulation status remained unaffected . Despite this, immunohistochemical analysis was consistent with the immunohistochemical findings in human littoral cell angiomas, the lining cells gave positive reactions to vascular endothelial cell (vWF) and macrophage (MSR-A) markers.

2.7 Neoplasia of the Central and Peripheral Nervous System

While spontaneous neoplasia of the central and peripheral nervous systems is a rare event in nonhuman primates, tumors of the CNS caused by radiation, or viral infections are more common (Miller et al 2012). The majority of radiation-induced tumors in the CNS are high-grade astrocytomas, specifically glioblastoma multiforme, which have been commonly detected in the brain and spinal cord of rhesus macaques and baboons. In addition to radiation-induced tumors, viral-associated neoplasia of the central nervous system (CNS) is also documented,

although less frequently. For example, in simian immunodeficiency (SIV) positive rhesus macaques, simian virus 40 (SV40) has been directly isolated from cases of malignant astrocytoma and oligodendroglioma. Furthermore, simian retrovirus D-infected cynomolgus macaques have been found to develop intracranial lymphomas, and LCV infection has been implicated in both localized and disseminated forms of CNS lymphoma. Although spontaneous neoplasia is a rare event, they have been reported sporadically in nonhuman primates. Apart from the radiation-induced glioblastoma multiforme, several spontaneous cases have also been recorded in baboons. In addition, baboons are also prone to developing other spontaneous central nervous system tumors, such as choroid plexus lipoma and medulloblastoma. However, in macaques spontaneous CNS tumors are less common, but include a fibrillary astrocytoma in a cynomolgus macaque and a neurohypophyseal astrocytoma in a rhesus macaque. Spontaneous CNS neoplasms are equally as rare in New World primates as Old-World primates and there are solitary reports of a primitive neuroectodermal tumor in a squirrel monkey and a melanocytic ependymoma in a Goeldi's marmoset. Lastly, tumors of the peripheral nervous system are extremely uncommon. They have been able to induce peripheral nerve tumors in rhesus macaques following the inoculation of the carcinogen methylnitrosourea.

3.0 Treatments and Prognosis

Despite the remarkable similarity between human and nonhuman primate neoplasms, there is a significant knowledge gap in the clinical management of spontaneous and experimentally induced neoplasms in nonhuman primates (Miller et al., 2012). Given the close similarity between human and nonhuman primate neoplasms, it is logical to conclude that diagnostic and therapeutic approaches developed for humans and domestic animals can be adapted for use in nonhuman primates. In light of the growing focus on captive breeding and maximizing the value of existing nonhuman primate populations, recognizing, and treating neoplastic diseases is essential to improve animal well-being, maximize the value of existing populations, and protect endangered wild species that are vital to biomedical research. A key approach to mitigating the risk of neoplasia in nonhuman primates is to prevent or reduce exposure to established etiologic agents. The knowledge gained from studying viruses that induce immunosuppression in both human and nonhuman primates provides a foundation for developing effective prevention strategies. For example, in a study assessing the efficacy of a vaccine protection against the EBV- induced lymphoma, the animal model established for the EB virus-induced malignant disease was the cotton-ton tamarin (Morgan et al., 1988). It had already been demonstrated that inoculation with a large dose of EB

virus invariably leads to the development of multiple tumors 2-3 weeks afterwards, therefore providing an ideal system for assessing the efficacy of vaccine protection intended to reduce the incidence of human tumors associated with EB virus infection. Cottontop tamarins were successfully vaccinated with gp340, the major envelope glycoprotein of Epstein-Barr virus, it was incorporated into immune-stimulating complexes (iscoms) and demonstrated 100% protection against a lymphoma-inducing dose of the virus.

In human oncology, cancer cachexia is a prevalent condition that often accompanies various types of cancer, characterized by a progressive wasting away of adipose tissue and skeletal muscle mass (Miller et al.,2012). This weight loss, which is a significant predictor of prognosis in human patients, is likely to occur in nonhuman primates as well. In a report review of eleven new cases of gastrointestinal neoplasia in nonhuman primates, clinical signs were seen in nine of the eleven monkeys, with the most common being weight loss and poor appetite (DePaoli et al., 1982). In human medicine, cancer cachexia is frequently accompanied by anorexia in patients, which can be attributed to the tumor's cytokine production, changes in taste sensation, and an imbalance between appetite-inducing and appetite-suppressing factors (Miller et al., 2012). Upon recognizing a sign or symptom that may suggest the presence of neoplastic disease in an animal, a thorough physical examination is crucial to assess all accessible areas of the body and identify any potential abnormalities and the emphasis and time spent on certain areas of the examination are determined from the history and initial visual observations. The physical examination should always involve a systematic palpation and visual inspection of the regional lymph nodes that drain the area where the suspected neoplasm is located. If the suspected neoplasm is accessible, a biopsy sample is obtained through incision or excision for diagnostic purposes, treatment monitoring, and obtaining living cells for further study. This diagnostic procedure is also mirrored in humans, while there is no single test that can definitively diagnose cancer in humans, a complete patient evaluation usually requires a meticulous review of medical history, a thorough physical examination, and multiple diagnostic tests (Treatments. Stanford Health Care et al., 2017).

In general, sampling procedures involve the collection of abnormal fluid from body cavities or the acquisition of cells from solid tumor masses through fine-needle aspiration, impression smears, or tissue scrapings (Miller et al., 2012). Fine-needle aspiration can significantly aid in accurate staging and grading and is a vital diagnostic tool. Cytodiagnosis can be significantly aided by the employment of monoclonal antibodies, immunohistochemical techniques, cytochemical stains, and flow cytometry. Immunohistochemistry has become a valuable diagnostic tool in nonhuman primates, enabling accurate identification of tumor origin and the detection of infectious agents. Information and results acquired from these diagnostic and sampling procedures can be used to

develop an accurate state of cancer, and this is crucial as it directly influences the development of treatment plans. Cancer staging enables the evaluation of the extent to which a neoplasm has metastasized beyond its original location. Stage I cancer is limited to the primary site, with no evidence of invasion into adjacent tissues. Stage II cancer has begun to infiltrate nearby tissues, while Stage III cancer has spread extensively into these areas. Stage IV cancer has metastasized to distant parts of the body (Miller et al., 2012). Additionally, it is essential to recognize that once a stage is assigned and treatment is initiated, the clinical stage remains unchanged even if disease recurrence or progression occurs in the future.

In the treatment of nonhuman primates with neoplasia, clinicians may draw upon a range of traditional anticancer strategies already employed in human and veterinary medicine, including surgical excision, radiation therapy, chemotherapy, immunotherapy, and other modalities (Miller et al 2012). For example, at the Southwest National Primate Research Center two baboons received treatment for squamous cell carcinoma (Haddad et al., 2009). Where, one tumor was surgically removed, but recurred within 5 months and the other baboon received intralesional chemotherapy but died during the course of the treatment. Another example is the surgical excision of intestinal tumors due to adenocarcinomas in fourteen rhesus macaques at the Wisconsin National Primate Research Center (Simmons et al., 2011). Survival after excision, along with lymph node invasion at biopsy and tumor recurrence at necropsy are reported in the table below.

Survival Time After Surgical Excision of Intestinal Neoplasia (n = 14)

Survival time (months)	*Number of monkeys*	*Lymph node invasion at biopsy*	*Tumor recurrence at necropsy*
<6	6	3	3
6	1	0	0
12	2	1	2
18	1	1	0
24	1	0	1
30	1	0	0
>48	2	0	1

Table 4. Survival time after surgical excision of14 intestinal neoplasia in rhesus macaques at the WNPRC (Simmons et al., 2011).

Although, six monkeys died within 6 months of surgery, none of them showed signs of the anastomosis site failing to heal properly. An additional three monkeys are currently alive at 16-, 28, and 29-months post-surgery. However, it is also essential to explore novel and experimental

treatments that have shown efficacy in human oncology and may be beneficial for nonhuman primate patients.

Conclusion

The complexity of neoplasia in nonhuman primates is exemplified by the intricate interplay of genetic, environmental, and constitutional factors that contribute to its development. This multifaceted disease process shares striking similarities with human cancer, highlighting the importance of understanding the underlying mechanisms.

Age is a significant determinant of spontaneous neoplasia, with an increasing incidence observed in older rhesus macaques, mirroring the pattern seen in humans. The study reviewed demonstrated that tumors occurred in animals over 20 years with the most prevalent type being adenocarcinoma of the large intestine.

Hereditary studies of cancer in nonhuman primates have also shown that pheochromocytomas in cotton-top tamarins may have a genetic link after pedigree analysis was executed. Further demonstrating the importance of genetic factors in the development of cancer and highlighting the potential for hereditary transmission of cancer

Environmental factors, such as chemical carcinogens, radiation, and viral infections, are also implicated in neoplasia development. Exposure to chemical carcinogens can lead to genetic and epigenetic changes, increasing the risk of tumor development. Radiation carcinogenesis has been linked to the development of benign and malignant tumors in multiple organ systems, while viral infections can cause malignant cell transformation and neoplasia.

Moreover, the frequency of reported neoplasms varies across different organ systems, which may be attributed to underreporting or genuine differences in tumor incidence between species. Despite the similarities between human and nonhuman primate neoplasms, there remains a significant knowledge gap in the clinical management of spontaneous and experimentally induced neoplasms in nonhuman primates. Nevertheless, it is logical to conclude that diagnostic and therapeutic approaches developed for humans and domestic animals can be adapted for use in nonhuman primates given their close similarities with human cancer.

Bibliography

1. Hill, C.K., Kumar, P. (2011). Radiation Carcinogenesis. In: Schwab, M. (eds) Encyclopedia of Cancer. Springer, Berlin, Heidelberg. https://doi.org/10.1007/978-3-642-16483-5_4898
2. John B. Little, Radiation carcinogenesis, *Carcinogenesis*, Volume 21, Issue 3, March 2000, Pages 397–404, https://doi.org/10.1093/carcin/21.3.397
3. What are neoplasia, tumors and cancer? how common ... (n.d.). http://publichealth.lacounty.gov/vet/docs/CancerAnEng.pdf
4. Deycmar S, Gomes B, Charo J, et al Spontaneous, naturally occurring cancers in non-human primates as a translational model for cancer immunotherapy Journal for ImmunoTherapy of Cancer 2023;11:e005514. doi: 10.1136/jitc-2022-005514
5. Brown SL, Anderson DC, Dick EJ Jr, Guardado-Mendoza R, Garcia AP, Hubbard GB. Neoplasia in the chimpanzee (Pan spp.). J Med Primatol. 2009 Apr;38(2):137-44. doi: 10.1111/j.1600-0684.2008.00321.x. PMID: 19367738; PMCID: PMC2893876
6. V. Caracciolo, A. Giordano, 14.12 - Viruses and Carcinogenesis, Editor(s): Charlene A. McQueen, Comprehensive Toxicology (Second Edition), Elsevier, 2010, Pages 1-13, ISBN 9780080468846, https://doi.org/10.1016/B978-0-08-046884-6.01413-5.
7. Chen Y, Williams V, Filippova M, Filippov V, Duerksen-Hughes P. Viral carcinogenesis: factors inducing DNA damage and virus integration. Cancers (Basel). 2014 Oct 22;6(4):2155-86. doi: 10.3390/cancers6042155. PMID: 25340830; PMCID: PMC4276961.
8. Andrew D. Miller, Chapter 6 - Neoplasia and Proliferative Disorders of Nonhuman Primates, Editor(s): Christian R. Abee, Keith Mansfield, Suzette Tardif, Timothy Morris, In American College of Laboratory Animal Medicine, Nonhuman Primates in Biomedical Research (Second Edition), Academic Press, 2012, Pages 325-356, ISBN 9780123813664, https://doi.org/10.1016/B978-0-12-381366-4.00006-7
9. Lynn Wachtman, Keith Mansfield, Chapter 1 - Viral Diseases of Nonhuman Primates, Editor(s): Christian R. Abee, Keith Mansfield, Suzette Tardif, Timothy Morris, In American College of Laboratory Animal Medicine, Nonhuman Primates in Biomedical Research (Second Edition), Academic Press, 2012, Pages 1-104 ISBN 9780123813664, https://doi.org/10.1016/B978-0-12-381366-4.00001-8
10. Edith E. Sproul, Richard S. Metzgar, James T. Grace; The Pathogenesis of Yaba Virus-induced Histiocytomas in Primates. *Cancer Res* 1 June 1963; 23 (5): 671–675

11. Fickenscher H, Fleckenstein B. Herpesvirus saimiri. Philos Trans R Soc Lond B Biol Sci. 2001 Apr 29;356(1408):545-67. doi: 10.1098/rstb.2000.0780. PMID: 11313011; PMCID: PMC1088444.
12. Kerstin Mätz-Rensing, Martina Bleyer, Chapter 15 - Viral Diseases of Common Marmosets,Editor(s): Robert Marini, Lynn Wachtman, Suzette Tardif, Keith Mansfield, James Fox, In American College of Laboratory Animal Medicine, The Common Marmoset in Captivity and Biomedical Research, Academic Press, 2019, Pages 251-264, ISBN 9780128118290, https://doi.org/10.1016/B978-0-12-811829-0.00015-7. (https://www.sciencedirect.com/science/article/pii/B9780128118290000157)
13. Barbara L. Parsons, Many different tumor types have polyclonal tumor origin: Evidence and implications, Mutation Research/Reviews in Mutation Research Volume 659, Issue 3, 2008, Pages 232-247, ISSN 1383-5742, https://doi.org/10.1016/j.mrrev.2008.05.004. (https://www.sciencedirect.com/science/article/pii/S1383574208000768)
14. Haddad JL, Dick EJ Jr, Guardado-Mendoza R, Hubbard GB. Spontaneous squamous cell carcinomas in 13 baboons, a first report in a spider monkey, and a review of the non-human primate literature. J Med Primatol. 2009 Jun;38(3):175-86. doi: 10.1111/j.1600-0684.2009.00338.x. PMID: 19220686; PMCID: PMC2919327.
15. Farman CA, Benirschke K, Horner M, Lappin P. Ovarian Choriocarcinoma in a Rhesus Monkey Associated with Elevated Serum Chorionic Gonadotropin Levels. Veterinary Pathology. 2005;42(2):226-229. doi:10.1354/vp.42-2-226
16. Miller AD, Masek-Hammerman K, Dalecki K, Mansfield KG, Westmoreland SV. Histologic and immunohistochemical characterization of pheochromocytoma in 6 cotton-top tamarins (Saguinus oedipus). Vet Pathol. 2009 Nov;46(6):1221-9. doi: 10.1354/vp.09-VP-0022-M-FL. Epub 2009 Jul 15. PMID: 19605896; PMCID: PMC2825153.
17. Adrian Vella, Robert A. Rizza, F. John Service, 238 - Hypoglycemia and Pancreatic Islet Cell Disorders, Editor(s): Lee Goldman, Andrew I. Schafer, Goldman's Cecil Medicine (Twenty Fourth Edition), W.B. Saunders, 2012, Pages 1499-1505, ISBN 9781437716047, https://doi.org/10.1016/B978-1-4377-1604-7.00238-4. (https://www.sciencedirect.com/science/article/pii/B9781437716047002384)
18. DePaoli A, McClure HM. Gastrointestinal Neoplasms in Nonhuman Primates: A Review and Report of Eleven New Cases. Veterinary Pathology. 1982;19(7_suppl):104-125. doi:10.1177/030098588201907s08

19. Brown SL, Anderson DC, Dick EJ Jr, Guardado-Mendoza R, Garcia AP, Hubbard GB. Neoplasia in the chimpanzee (Pan spp.). J Med Primatol. 2009 Apr;38(2):137-44. doi: 10.1111/j.1600-0684.2008.00321.x. PMID: 19367738; PMCID: PMC2893876.
20. Lowenstine LJ, McManamon R, Terio KA. Apes. Pathology of Wildlife and Zoo Animals. 2018:375–412. doi: 10.1016/B978-0-12-805306-5.00015-8. Epub 2018 Oct 26. PMCID: PMC7173580.
21. Slayter MV. Nasal cavity carcinosarcoma in a bonnet macaque (Macaca radiata). J Med Primatol. 1988;17(1):49-56. PMID: 3367358.
22. Yamate J, Izawa T, Kuwamura M, Mitsunaga F, Nakamura S. Vasoformative Disorder, Resembling Littoral Cell Angioma, of the Spleen in a Geriatric Japanese Macaque (Macaca fuscata). Veterinary Pathology. 2009;46(3):520-525. doi:10.1354/vp.08-VP-0228-Y-CR
23. Morgan AJ, Finerty S, Lovgren K, Scullion FT, Morein B. Prevention of Epstein-Barr (EB) virus-induced lymphoma in cottontop tamarins by vaccination with the EB virus envelope glycoprotein gp340 incorporated into immune-stimulating complexes. J Gen Virol. 1988 Aug;69 (Pt 8):2093-6. doi: 10.1099/0022-1317-69-8-2093. PMID: 2841417.
24. Treatments. Stanford Health Care. (2017, September 12). https://stanfordhealthcare.org/medical-conditions/cancer/cancer/cancer-treatment.html
25. Simmons HA, Mattison JA. The incidence of spontaneous neoplasia in two populations of captive rhesus macaques (Macaca mulatta). Antioxid Redox Signal. 2011 Jan 15;14(2):221-7. doi: 10.1089/ars.2010.3311. Epub 2010 Oct 28. PMID: 20524847; PMCID: PMC3014768.
26. Causes. Stanford Health Care. (2017a, September 12). https://stanfordhealthcare.org/medical-conditions/cancer/cancer/cancer-causes.html
27. Richard E. Weller, Chapter 4 - Neoplasia/Proliferative Disorders, Editor(s): B. Taylor Bennett, Christian R. Abee, Roy Henrickson, In American College of Laboratory Animal Medicine, Nonhuman Primates in Biomedical Research, Academic Press, 1998, Pages 207-232, ISBN 9780120886654, https://doi.org/10.1016/B978-012088665-4/50006-3.
28. Wednesday, A. 31. (2022, August 31). Cancer genes in humans vs. chimps: Why are we more susceptible?. Memorial Sloan Kettering Cancer Center. https://www.mskcc.org/news/cancer-genes-humans-vs-chimps-why-are-we-more-susceptible