Fat Facts on Cancer: Canine Obesity & Cancer Prevalence

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Introduction

Obesity prevalence in the human population has increased for the last fifty years (Flegal KM, *et al.* 2002; Ogden CL, *et al.* 2004). Obesity in humans is defined as having a body mass index (BMI) greater than 20% over ideal and is associated with a number of adverse health effects, including degenerative joint disease, intervertebral disc disease, respiratory compromise, and increased risk of mortality from other diseases (Calle EE, *et al.* 1999; Calle EE & Thun MJ 2004). As of the year 2004, two-thirds of adult humans in the United States are estimated to be overweight or obese based on BMI measurements (Ogden CL, *et al.* 2006). Excess weight not only introduces mechanical stress to skeletal and soft tissue structures, but adipocytes are metabolically active resulting in a chronic inflammatory condition (Cottam DR, *et al.* 2004; Zou C & Shoa J 2007) that can predispose the individual to certain cancers, such as colorectal carcinoma (Wei EK, *et al.* 2004), postmenopausal breast adenocarcinoma (van den Brandt PA, *et al.* 2000), and uterine leiomyomas (Takeda T, *et al.* 2008).

There are over 72 million dogs in households across the United States (AVMA 2007). Of those, an estimated 34% (Lund EM, *et al.* 1999) to 40% (Weeth LP, *et al.* 2007) may be considered overweight or obese and some researchers have proposed that canine obesity prevalence is increasing along with human obesity trends (German AJ 2006). Excess fat mass in dogs has a significant impact on the development of degenerative orthopedic disease (Kealy RD, *et al.* 2002) and insulin-resistance (Mattheeuws D, *et al.* 1984); it has also been associated with decreased longevity (Kealy RD, *et al.* 2002) and increased prevalence of benign and malignant neoplasms (Lund EM, *et al.* 2006).

Obesity Facts

Positive energy balance occurs when an animal's energy intake exceeds energy demand and obesity occurs when the individual dog is allowed to become more than 20% over its ideal body weight (Mawby DI, *et al.* 2004). This alteration in energy balance can result from a number of potentially interrelated events. Energy requirements may vary with breed (Edney AT & Smith PB, 1986; McGreevy PD, *et al.* 2005), neuter status (Fettman MJ, *et al.* 1997; Jeusette I, *et al.* 2004), and certain medical conditions such as hypothyroidism. Husbandry issues including lack of exercise, readily available and palatable foods, and food substituted for attention and affection by owners may also result in weight gain among pets.

Clinical measures of obesity status evaluate the degree of adiposity relative to the lean musculoskeletal system of the individual dog. In a veterinary setting, the most practical and common measure is a body condition score (BCS). There are two BCS scales in common use, a 5-point scale with 3 out of 5 considered ideal and a 9-point scale with 4 to 5 out of 9 considered ideal. Each point on a 9-point scale represents a 10-15% difference in body weight (Laflamme, *et al.* 1994); therefore animals with a BCS of 7 out of 9 or greater would be considered obese.

Metabolic Syndrome

The ability of adipocytes to secrete cytokines (adipokines) and inflammatory markers into circulation has been well documented in people (Cottam DR, *et al.* 2004; Zou C & Shoa J 2007) and may set the stage for future metabolic derangement. Hormones and cytokines such as leptin, resistin, adiponectin, IL-6, TNFα, and retinol-binding protein are secreted by adipocytes and, either independently or in concert, act to induce peripheral insulin-resistance, inhibit normal apoptotic mechanisms, promote angiogenesis, and decrease circulating levels of high-density lipoproteins (Zou C & Shoa J 2007). The presence of chronic inflammation has been proposed to result in oxidative injury to DNA and predispose obese individuals to increased cancer risk (Cowey S & Hardy RW 2006).

Obese dogs have increased circulating levels of adipokines, such as insulin-like growth factor (IGF), TNFα and leptin (Gayet C, *et al.* 2004; Martin LJM, *et al.* 2006; Ishioka K, *et al.* 2002). Leptin is an *in vitro* promoter of mammary tumors (Yin N, *et al.* 2004; Chen C, *et al.* 2006) and hepatocellular carcinomas (Wang XJ, *et al.* 2004) in humans; to date, this relationship has not been documented in dogs. Tumor suppressor genes, such as p53, are found in about half of all human cancers (Chang F, *et al.* 1993) as well as certain canine cancers, such as mammary tumors (Lee CH, *et al.* 2002) and osteosarcoma (Johnson AS, *et al.* 1998). Transgenic p53 knockout mice that are allowed to become obese through excess energy intake have more of an accelerated tumor development than lean cohorts (Berrigan D, *et al.* 2002). Elevated levels of leptin can directly inhibit p53 expression in human mammary cancer cells *in vitro* (Chen C, *et al.* 2006).

Cancer Facts

Cancer is a leading cause of death in dogs over 10 years of age (Bronson RT, 1982). Cancer results from DNA damage that allows the aberrant cell to grow without normal apoptotic triggers (absence of regulatory controls), confers the ability of the aberrant cell to induce angiogenesis (acquire nutrients for survival), and allows the proliferated cells to be locally invasive or metastatic (spread beyond normal tissue boundaries). Accumulation of environmental toxins, oxidative damage (both endogenous and exogenous), and genetic factors affecting cell repair mechanisms may also contribute to cancer development.

Canine Obesity and Cancer

There are a limited number of retrospective studies that have evaluated the correlation of specific cancer types and obesity prevalence in dogs (Glickman LT, *et al.* 1989; Sonnenschein EG, *et al.* 1991; Perez Alenza D, *et al.* 1998; Philibert, *et al.* 2003). Glickman *et al.* (1989) collected owner-reported obesity status 1-year prior to diagnosis of transitional cell carcinoma of the urinary bladder of dogs and found that there was an increased prevalence of obesity compared with non-cancer controls. Sonnenschein *et al.* (1991) and Perez Alenza *et al.* (1998) found a positive correlation between mammary tumor development and owner-reported obesity, but when body weight records were compared to breed standards for affected animals, there was no correlation. Philibert *et al.* (2003) only used documented body weight versus breed standard and also found no correlation with obesity and mammary tumor development. The positive correlations seen in the earlier studies may be attributed to over reporting of conditions and behaviors believed to influence a specific disease state; this "recall bias" is a documented occurrence in human nutritional epidemiology (Willet W 1998).

Mortality data from a long-term prospective study on calorie restriction showed an equal distribution of cancers among control (mean BCS 6.7 out of 9) and restricted-fed (mean BCS 4.6 out of 9) Labrador retrievers (Lawler DF, *et al.* 2005). The variety

of cancer types reported, limited sample size (48 dogs), and the avoidance of overt obesity in control dogsmake direct conclusions about obesity and cancer development in that study difficult.

A recent BCS survey of 100 canine cancer patients found that 26 dogs were considered overweight and 29 dogs were considered obese using a 9-point BCS scale (Michel KE, *et al.* 2004). The Michel *et al.* (2004) study was focused on cancer cachexia and as such associations between obesity and cancer prevalence cannot be made based on the study design and sample size.

Two larger scale epidemiological veterinary studies were conducted in the United States and published in recent years. Lund *et al.* (2006) surveyed dogs that presented to a number of veterinary practices across the country and found that obese dogs had an increased prevalence of benign and malignant neoplasms when compared to lean dogs. A retrospective study of dogs presenting to a referral veterinary teaching hospital showed a lower prevalence of obesity among dogs when all types of malignant neoplasms were evaluated together (Weeth LP, *et al.* 2007), but a difference in obesity prevalence when cancer types were evaluated individually. Most notably, Weeth *et al* (2007) found a higher prevalence of overweight and obese (BCS $\geq$ 6 out of 9) dogs diagnosed with mammary cancers compared to non-cancer controls, though this finding was not statistically significant due to small sample size (49 dogs).

Summary

Caloric restriction and avoidance of weight gain have been shown in both human and veterinary literature to increase lifespan and decrease disease incidence. The current body of knowledge on obesity and canine cancer development is provocative, but direct evidence showing obesity as a promoter of cancer development in dogs is lacking. Despite this, there are a number of documented health benefits to avoiding obesity in dogs and obesity prevention and treatment should be routine in veterinary practice. The recording of body condition in addition to weight measurements is strongly recommended to identify at-risk individuals and to increase owner awareness of obesity as a true medical condition. Documentation of BCS may also help define the relationship of obesity and cancer development for future epidemiological studies. Obesity is not a cosmetic issue and, unlike environmental or genetic influences on disease, is within human control.

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