Bovine Ocular Squamous Cell Carcinoma: An Epidemiological Perspective

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ABSTRACT

Epidemiological studies on bovine ocular carcinoma were reviewed. Reports on the frequency and the distribution of the disease indicate that it is still a very prevalent and economically important disease. It is recognized throughout North America, but is more frequent in lower latitudes under range conditions. Etiological factors including ultraviolet light, circumocular apigmentation and viruses, as well as the pathogenesis, are considered in light of current knowledge on carcinogenesis of this tumor. It is likely that the induction of bovine ocular carcinoma is multifactorial and the precise roles played by each of the various factors are not yet understood.

Key words: Bovine ocular squamous cell carcinoma, epidemiology, frequency and distribution, susceptibility, etiological factors, pathogenesis.

RÉSUMÉ

Cet article présente une revue des études épizootiologiques, relatives à l'épithélioma spinocellulaire oculaire bovin. Les rapports sur la fréquence et la distribution du néoplasme révèlent qu'il est commun et revêt une importance économique. Il sévit partout en Amérique du Nord, surtout en basses latitudes et dans les ranchs. Les auteurs commentent, à la lumière de nos connaissances actuelles sur la carcinogénèse de ce néoplasme, sa pathogénèse et ses divers facteurs étiologiques, à savoir: les rayons ultraviolets, l'absence de pigmentation périoculaire et les virus. Il semble que le développement de l'épithélioma spinocellulaire oculaire bovin dépende de plusieurs facteurs dont le rôle individuel demeure toujours obscur.

Mots clés: épithélioma spinocellulaire oculaire bovin, épizootiologie, fréquence et distribution, susceptibilité, facteurs étiologiques, pathogénèse.

INTRODUCTION

Bovine ocular squamous cell carcinoma (BOSCC) is the most common malignant tumor affecting cattle in North America. Control of this disease would be of economic significance to the beef and dairy cattle industries.

Characteristically BOSCC is an invasive chronically progressing tumor which metastasizes through draining lymphatics of the head and neck. It is a disease of high morbidity which results in economic loss through early culling and carcass condemnation at slaughter. Typically, the carcinoma arises from plaque and papilloma precursor lesions on and around the epithelium of the eye. These lesions occur most commonly at the corneoscleral junction and on the lower eyelid.

Several studies have been concerned with the pathogenesis of BOSCC in an effort to better define the etiology of the disease. In addition, BOSCC has proven to be a convenient model from which many therapeutic procedures have been described. A recent review has summarized these findings (1) however, the epidemiology of BOSCC remains poorly defined. The purpose of this paper is to discuss the distribution and the determinants of BOSCC as they are known to affect cattle populations. Epidemiological data is summarized in an attempt to define more precisely the etiological factors of this disease in order that rational decisions for the study, prevention and control of BOSCC can be made.

The majority of studies on BOSCC have been observational studies. Only a limited number of controlled experiments have been performed in an attempt to define the determinants of BOSCC. In an epidemiological sense, determinants are those factors which influence health and disease. They include any factor which, when altered, produces a change in the frequency or characteristics of the disease (2). Much of the information on the incidence of BOSCC has been derived from studies based on records or pathological submissions from federally inspected abattoirs.

FREQUENCY OF THE DISEASE

Abattoir surveys provide some insight into the relative importance of this disease based on proportional morbidity rates. Russell *et al* (3) reported that 82% of condemnations for neoplasia at slaughter were due to BOSCC. These high rates have been supported by other studies in the United States (4). Records from US federally inspected packing houses estimated that 12.6% of all bovine carcasses condemned were due to BOSCC (5). In Canada, nationwide estimates of slaughterhouse studies have not accurately estimated the prevalence of BOSCC. Since these lesions are easily recognized on gross examination they are often not submitted for histopathological interpretations and hence not included in such studies (6,7). However, an independent abattoir survey in Alberta included BOSCC lesions and estimated that 66% of condemnations for neoplasia in that province were due to this dis-

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ease. Twelve percent of all condemnations in Alberta were due to BOSCC (8), which correlates well with previous US reports (5).

The incidence and/or prevalence of BOSCC has been reported in numerous studies. However, the actual incidence rate in cattle herds is often difficult to assess. Estimates based on slaughterhouse data vary from 0.2% to 0.98% (3,4,8). Prospective studies on herds or retrospective studies using herd records demonstrate considerably higher rates, ranging from 4.4% to 5.6% (9,10,11,12,13). However, many of these studies considered herds of Hereford or Hereford cross cattle only and hence it is difficult to extrapolate from them.

Many factors influence the results of investigations of tumor frequency, particularly in abattoir studies which generally provide prevalence data. Care is needed in the interpretation of these conclusions since the actual incidence may be higher. For example, some tumors are removed or treated by veterinarians and are not recorded in slaughtered animals. As well, natural deaths and disposal by producers may occur and many older debilitated cows may be preferentially shipped to nonfederally inspected abattoirs. Studies which were based on gross identification rather than histopathological confirmation of BOSCC may also be misleading. As well, up to 50% of precursor lesions in younger animals may spontaneously regress (14).

Russell *et al* (3) estimated that actual incidence rates may be as high as two to four times the prevalence that standard slaughterhouse data would indicate. The time of year (cows are culled after calves are weaned in the fall), the age of cattle, the breed and the type of beef animal processed per plant and the geographical region the survey was taken in, are all important causes for variations in incidence.

The major intrinsic host factors of descriptive epidemiology are age, sex and breed. The occurrence of disease at different levels of these factors is best described by the use of incidence rates. These figures provide estimates of the risk (probability) of disease occurrence with different levels of these factors (15).

Most breeds of cattle are susceptible to BOSCC, but it is well established that the Hereford breed and Hereford crosses are more commonly affected. French (14) examined over 300 mature cattle, 150 were Shorthorn and the remainder were Hereford; among the Herefords he observed over 35% with tumors or precursor lesions, but no eye lesions occurred in the Shorthorn cattle inspected. Anderson (16) presented data on nearly 1,500 cattle of six different breeds and various Hereford crosses. Of 696 purebred Herefords in this group, 25.3% had "cancer eye" or early lesions. Only 17.7% of 261 Hereford crosses and one Holstein out of 140 were observed with the disease. Purebred Herefords accounted for 48.3% of the negative population and no tumors were found in Angus, Shorthorn, Santa Gertrudis, or Scottish Highland cattle (16).

Other reports confirm that Herefords have the highest incidence (13). However, the interpretation of these statistics must consider that Herefords outnumber all other breeds of range cattle (3). Cases of BOSCC have been reported in Holstein-Friesian, Guernsey and Shorthorn cattle (17), Ayrshire, Brahman, Brown Swiss, Hollandensa, Javenese-Mongolian, Jersey, Normandy cattle (3) and others (1).

Age, as with many other cancers, is an important determinant. Cases of BOSCC are extremely rare in younger cattle; BOSCC occurs primarily in aged cows. In studying the disposal records of cattle over a 21 year period, Blackwell *et al* (18) reported finding no cases of BOSCC in cattle less than four years of age. The rate of culling appears to increase linearily with age until a peak age of incidence between seven and nine years of age (3,5,16,19). The decline in the incidence rate after this peak may be due to a genetic predisposition (19) or to managerial culling practices (5).

It is not known whether the sex of the animal is an important factor in this disease. The apparently greater prevalence of BOSCC in cows results from a normal sex-age imbalance in herds of cattle. For economic reasons steers are sent to slaughter, while young and mature cows are kept for breeding and stay in the herd as long as they remain productive and healthy. Since the disease is most prevalent in older cattle, the majority of cases are naturally among cows. There is no scientific data to suggest that females are more susceptible to BOSCC than males of the same age.

DISTRIBUTION OF THE DISEASE

Many indications concerning the etiology of BOSCC have been provided by the geographical distribution of the disease. The occurrence of BOSCC has been reported worldwide, in Europe (20), Asia (21), Africa (22), Australia (14) and South America (23). The majority of studies, however, have been made in North America (3,8,13,16,17,18,24).

The frequency of BOSCC in the USA is higher in the southwestern region, geographically in lower latitudes with higher levels of sunlight (3,10,16). Similarly in Australia, the frequency of BOSCC is higher in tropical than in temperate climates (14), following a pattern similar to that shown for human skin cancer. Lower incidence rates of BOSCC, as found in the United Kingdom and other European countries, have been mentioned (1,3,20). The distribution of range cattle is not, however, geographically uniform. For example, in Canada the majority of beef cows populate ranges in the western provinces and this needs to be considered when describing geographic risk of BOSCC.

INTERRELATIONSHIPS BETWEEN HEALTH, DISEASE AND SUSCEPTIBILITY

In considering the epidemiology of the disease, many details may be obtained by contrasting the characteristics of herds having a relatively high frequency of tumors to herds having a lower frequency of BOSCC.

As noted, many investigators have reported an increasing prevalence of this condition with increasing age (5). While the age pattern may reflect only a need for prolonged exposure to carcinogens, it may also indicate biochemical or immunological alterations which increase with age.

The deterioration of functional body systems such as those controlling electrolyte balance, urea level and protein synthesis or hemopoiesis impair the capacity of animals to resist neoplastic disease. Exogenous substances (such as drugs), or endogenous hormonal imbalances (glucocorticoids

(25)) may have generalized, nonspecific immunosuppressive effects. Other factors which may influence the hosts general immunosurveillance and must be considered besides age are: concurrent disease, stress, dietary and biochemical deficiencies.

In an attempt to identify biochemical defects in susceptible animals, Cleaver *et al* (26) were unable to identify differences in susceptibility between Hereford and Angus cattle. By testing the hypothesis that BOSCC was similar to xeroderma pigmentosum, a DNA repair defect in humans, they were unable to demonstrate any difference in the capacity of fibroblasts from these two breeds to repair DNA damage induced by exposure to ultraviolet light.

Immunological investigations have demonstrated by lymphocyte stimulation tests that cattle with BOSCC are immunocompetent (27,28). Curiously, lymphocytes from carcinoma-bearing and carcinoma-free Herefords differed from Droughtmaster cattle (a breed with a low prevalence of BOSCC) in being more susceptible to ultraviolet irradiation (29). This may partially explain an increased prevalence, hence vulnerability, to this tumor in circumocular apigmented Herefords.

In a 20 year cohort study (16,30), high levels of nutrition were correlated with an increased incidence rate of BOSCC. Cattle maintained on a minimal nutrition level had a lower rate of BOSCC. Those maintained on high levels, not only had a higher incidence rate of tumors, but also a greater number of affected sites per animal, higher incidences at younger ages and developed more progressive disease (16). These findings indicate an apparent physiological effect of high levels of nutrition on tumor development. Interestingly enough, in a genetic study, cows which eventually developed ocular tumors, were not as heavy as others in the first two years of life. Roubicek and Ray (19) compared the past range performance weights of 155 cows which had developed ocular tumors to 250 cows in the same herd which did not have tumors. They demonstrated that on average, cattle destined to develop tumors, weighed less at a younger age (i.e. they weighed less at weaning and 20 months of age).

Susceptibility to BOSCC has been reported to be influenced by genetic factors (9,14,16,19,31) and that the Hereford breed is the most susceptible (4,9,13,14,18). However, specific genetic susceptibility for the Hereford breed has been questioned because of the past bias for Hereford cattle in the beef industry (3) where Hereford or Hereford cross-bred cattle outnumber all other range cattle. Genetic studies in BOSCC have been carried out to evaluate two major aspects of inheritance; specifically, inheritance of susceptibility independent of environment factors and the genetic relationship between eye pigmentation and BOSCC. In the past, most studies have reported on the interrelationship between environmental levels of ultraviolet light and epithelial pigmentation as discussed under etiological factors of disease.

To date, all genetic research on BOSCC concerned with the inbreeding of affected cattle, has concluded that offspring of affected sires and dams have a higher incidence rate of ocular lesions than contemporaries. The heritability of BOSCC has been estimated by several methods, based on parent offspring (3,5,9,13,18), paternal, maternal half-sib studies (5,13,18,19) and by breed comparisons (13,16,18,32). Since several methods have been used to estimate the heritability of susceptibility, an overall interpretation of these studies is difficult. However, the results of these studies consistently indicate a definite genetic influence. Russell *et al* (5) estimated the heritability of susceptibility by using incidence rates as well as the number of tumors per animal by the paternal half-sib method. Tumors of each affected cow were confirmed cytologically. Bovine ocular squamous cell carcinoma-affected sires within lines of cattle had a significant genetic effect on the development of BOSCC lesions among offspring (5). It has been estimated that 17 to 40 percent of the phenotypic variability in susceptibility to the disease is due to the additive genetic differences among cattle (5,9,29). Vogt *et al* (33) suggest that although a significant genetic influence exists, selection against the disease would be very difficult because of its late manifestation.

ETIOLOGICAL FACTORS AND PATHOGENESIS

The etiology of BOSCC is still poorly understood, however, it is obvious that the interaction of many factors is necessary for the sequential progression of benign states to squamous carcinoma (3). Of these, ultraviolet light (26,34), viruses (23,35, 36,37,38) and circumocular apigmentation (5,14) are thought to play major roles in the susceptibility, induction and promotion in the carcinogenesis of BOSCC (3).

Evidence for the participation of solar radiation is derived from observations on the inverse relationship between BOSCC and periocular epithelial pigment, the most obvious being eyelid pigment (9,10,14,31,39). Since cattle have either pigmented and nonpigmented periocular areas, the effect of ultraviolet radiation on tumor development in pigmented and nonpigmented epithelium can be compared. In a survey of 842 mature cattle (39), 17.6% with no lid pigmentation in either eye had tumor lesions. Individuals with partially pigmented lids had considerably fewer lesions and cattle with completely pigmented eyelids had acquired no BOSCC lesions. Observations on tumors which have developed in partially pigmented eyelids have concluded that lesions develop primarily in the unpigmented areas, but may soon encroach on pigmented areas as they enlarge (14,31).

Estimates of the heritability of eyelid pigmentation in cattle have been reported to be relatively moderate (33,39), indicating a genetic predisposition which could possibly be avoided by conscientious breeding practices. However, eyelid pigment itself does not afford protection of more susceptible corneoscleral epithelium (31,39), since medial and lateral areas remain exposed during sunlight hours. When cattle hold their heads in certain positions, the sun's rays focus at the lateral or medial limbus (40). Lesions arise most commonly at the corneoscleral junction (3,5,17) and more often at the lateral limbus than the medial side (5). Respectively, the lower eyelid, nictitating membrane and medial canthus are less commonly affected sites (3,5,17). Although limbal pigmentation is also heritable and appears to be genetically related to lid pigmentation (16,33,39),

it is not fully expressed as pigmented epithelium until five years of age or later (16). Hence, the inhibitory effect of corneoscleral pigment on the occurrence of BOSCC lesions at this site are not as obvious as the negative effect of lid pigment on lid tumors. Generally, breeds of cattle and individuals within breeds differ in the amount and locations of periocular pigmented epithelium. Any animal which lacks pigment around these particularly sensitive ocular sites is more prone to develop BOSCC lesions. Therefore, it is apparent that susceptibility to BOSCC is partially mediated through pigmentation. This is apparently influenced genetically. Thus, lack of pigmentation increases the vulnerability to the carcinogenic effect of actinic radiation.

Chronic exposure to short wavelength ultraviolet radiation, a component of sunlight, has been implicated in the predisposition to certain neoplasms in many species. In a retrospective study, Anderson and Skinner (10) classified nine different herds, totalling nearly 5,000 Hereford cattle into their geographical/environmental groups based on altitude, latitude and annual hours of sunlight. Each group of three herds was further subdivided into low, medium and high exposure herds based on levels of sunlight exposure. In each case, age-adjusted incidence rates for each herd corresponded to the levels of sunlight each received, the highest having the greatest incidence of BOSCC.

To further substantiate the carcinogenic effect of actinic radiation on BOSCC development, Kopeckey *et al* (34) treated four Hereford cows with daily doses of ultraviolet Beta radiation (UV-B). Two other cows were kept in the same controlled environment indoors but were not exposed to the daily dose of radiation. Virus isolation attempts were negative throughout the experiment. At the end of the one year period three out of four cattle had developed BOSCC lesions; no tumors were observed in the control cows. To date, no follow up studies have been reported.

The precise photocarcinogenic mechanisms of UV-B in BOSCC are unclear and can only be speculated upon at this time. As mentioned previously, DNA repair is not impaired in fibroblasts of BOSCC susceptible cattle (26). However, the production of cancer by UV radiation may be initiated through the efficient process of DNA repair, enabling the cell to survive DNA damage, but allowing errors in DNA replication to persist thus allowing for the possibility of subsequent malignant change (41). As well, reports are emerging which imply a significant effect of UV light impairing the host's immune system and ability to defend against tumor development (29,42,43,44). Finally, the phenomenon of a latent ultraviolet-induced viral activation and oncogenesis (45) may be a significant event in the pathogenesis of BOSCC.

Many other etiological determinants have been proposed in the past. Russell *et al* (3) noted that the irritating action of sand and dust, insects, occurrence of "pink eye" and chemical carcinogens as possible factors involved in the genesis of BOSCC. Indeed even eyeworms (*Thelazia* spp) (22,46) and vitamin A (3,47) have at one time been implicated as etiological factors. However, there is no concrete evidence, to date, to support the association of any of these specific factors with BOSCC development.

A viral etiology has been suspected for many years and several independent studies have demonstrated viruses (23,35,36,37,38) or virus-like particles in tumor tissue (48). In a study conducted by Taylor and Hanks (38), biopsy samples were collected from 32 animals in a Nevada abattoir. The tumors used in the study included corneal tumors in early and late stages, as well as tumors excised from nictitating membranes. The ratio of infectious bovine rhinotracheitis (IBR) virus isolates from these three sites of tumor were 9:16, 2:11 and 4:5 respectively. Attempts at isolating IBR virus from twenty normal eyes was not successful. Correlations of serum neutralizing titers against IBR in normal cattle and in cattle affected with eye tumors were also reported in this study. In the normal group, serum neutralizing antibody titers were detected in the sera of 29% of 96 animals tested. In the second group affected with BOSCC, serum neutralizing titers were observed in 84% of 19 animals tested. These results supported earlier observations of "herpes-type" inclusion bodies reported in histological studies of BOSCC lesions (3). Reports which identify an association between precursor plaque lesions and outbreaks of IBR in cattle support these findings (49). Alternately, this virus may be an incidental result of reduced resistance to viral infection in tumor-bearing animals.

Conversely, Anson *et al* (50) reported an inability to isolate viruses from 31 tissue homogenates of BOSCC. They concluded that previous isolation of IBR by other groups were simply of passenger viruses since most herpesvirus tumors yield infectious virus only after induction by UV light, steroids, or pH changes. This study did, however, demonstrate tumor cell-associated antigens which reacted to herpesvirus 5 (DN-599) antisera by indirect immunofluorescence on tumor cells grown in cell culture.

Isolations of latent IBR and DN-599 herpesviruses from the trigeminal ganglion of clinically normal cattle may be a significant observation for etiological consideration of BOSCC (51). Most recently papillomaviruses have been identified by electron microscopic examination of negatively stained preparations of precursor lesions of BOSCC (36).

A latent, ultraviolet light-activated viral etiology for BOSCC is an intriguing but unproven hypothesis. Viral isolations from ocular carcinoma or associated precursor lesions do not prove "cause" of the tumor. Indeed, not only viruses, but also bacteria, fungi and other parasitic agents are common contaminants of these tumors.

The pathogenesis of BOSCC is sequential, progressing through a series of benign and dysplastic states. These benign precursors may persist, spontaneously regress, or develop to malignant squamous carcinoma (3). Sequentially, the nonkeratinized stratified squamous epithelium of cornea and conjunctiva first develop into grossly detectable hyperplastic plaques which arise most frequently at the limbal area. Later, these plaques may progress into papillomas or proceed to carcinoma *in situ* and into invasive squamous cell carcinoma (1,3,17). Precursor lesions which develop on the lower eyelid usually arise at the mucocutaneous junction. So-called

keratomas arise from these areas of hyperkeratosis of the eyelid which histologically resemble hyperplastic plaques. Observations on the progression to papilloma at this site are rare. It is felt that because of the dense corneoscleral stroma, exophytic papillomas develop there rather than at the mucocutaneous junction of the eyelid where keratomas and more infiltrative acanthoses tend to preside. Variations in the gross appearance of the lesions at different periocular anatomical sites has led to considerable confusion in the nomenclature of BOSCC precursor states. The gross appearance is dependent on the anatomic location, which dictates the interaction between the affected epithelium and the underlying tissue. Despite these gross differences the lesion is consistently squamous hyperplasia with hyperkeratosis and acanthosis proceeding to dysplasia with fibroplasia and eventually, malignant transformation to squamous cell carcinoma. The precise stage or stages at which the putative etiological factors act in the process of malignant transformation are unknown at this time.

CONCLUSIONS

Epidemiological studies have provided many clues about the causes of neoplastic disease in general. As information on a disease is assimilated, such studies can be refined and redirected towards the high risk subpopulation from which a more accurate delineation of the etiological factors may be made. This process is made more difficult when there are a number of possible etiological parameters. It is at this point that various hypotheses must be tested with laboratory experiments and further analytical methods.

The primary subpopulation of cattle affected by BOSCC includes Hereford cows over five years of age with poorly pigmented circumocular epithelium, which are grazed in geographical areas with relatively high levels of actinic radiation. Briefly, the phenomenon of cancer occurring in older animals can be explained by the prolonged exposure required for the correct chance interaction by multiple factors required for tumorigenesis. Cows may be more commonly affected simply because of the female sex predominance in older cattle populations, not necessarily because of a sex predilection of BOSCC for females. Herefords are the breed most commonly affected by this disease, not only because they are the most common breed kept in an environment favorable for BOSCC development, but because they also have a strong genetic trait for white faces. The relationship between circumocular apigmentation and the chronic tumor-stimulating effect of actinic radiation is strong but evidence is not yet conclusive.

Finally, the controversy concerning viral oncogenesis in BOSCC is far from settled. Many possibilities exist as to the role such herpesviruses and/or papillomaviruses may play in the sequential development of benign precursors and their progression to squamous carcinoma. These suspicions have largely been supported by the phenomenon of tumor regression when allogenous BOSCC extracts are used. More seroepidemiological studies will have to be correlated with immunopathological and DNA hybridization studies before these hypotheses can be confirmed. To determine causation by epidemiological studies is difficult, however, information obtained from such studies has provided much insight and continues to provide parameters for more fundamental laboratory investigations.

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REFERENCES

1. **SPADBROW PB, HOFFMAN D.** Bovine ocular squamous cell carcinoma. Vet Bull 1980; 50: 449-459.
2. **KLEINBAUM DG, KUPPER LL, MORGENSTERN H.** Epidemiologic research, 1st ed. Belmont, California: Lifetime Learning Publication, 1982.
3. **RUSSELL WO, WYNNE ED, LOQUVAM GS.** Studies on bovine ocular squamous cell carcinoma (cancer eye). Cancer 1956; 9: 1-52.
4. **BRADLY PJ, MIGAKI G.** Types of tumors found by meat inspectors in an eight year survey. Ann NY Acad Sci 1963; 108: 872-879.
5. **RUSSELL WC, BRINKS JS, KAINER RA.** Incidence and heritability of ocular squamous cell tumors in Hereford cattle. J Anim Sci 1976; 43: 1156-1162.
6. **DUKES TW, BUNDZA A, CORNER AH.** Bovine neoplasms encountered in Canadian slaughterhouses: A summary. Can Vet J 1982; 23: 28-30.
7. **PLUMMER PJG.** A survey of six hundred and thirty-six tumors from domesticated animals. Can J Comp Med 1966; 20: 239-251.
8. **HAMIR AN, PARRY OB.** An abattoir study of bovine neoplasms with particular reference to ocular squamous cell carcinoma in Canada. Vet Rec 1980; 106: 551-553.
9. **ANDERSON DE.** Genetic aspects of bovine ocular carcinoma. Genetics and Cancer. The University of Texas Press, 1959.
10. **ANDERSON DE, SKINNER PE.** Studies on bovine ocular squamous cell carcinoma ("cancer eye"). XI Effects of sunlight. J Anim Sci 1961; 20: 474-477.
11. **GUILBERT HR, WAHID A, WAGNON KA, GREGORY PW.** Observations on pigmentation of eyelids of Hereford cattle in relation to occurrence of ocular epitheliomas. J Anim Sci 1948; 7: 426-429.
12. **KROX JH.** Occurrence of cancer eye in range cattle. N Mex Exp Sta, SW Forest and Range Exp Sta 1949: 12-13.
13. **WOODWARD RR, KNAPP B JR.** The hereditary aspects of cancer eye in Hereford cattle. J Anim Sci 1950; 9: 578.
14. **FRENCH GT.** A clinical and genetic study of eye cancer in Hereford cattle. J Anim Sci 1959; 9: 578-581.
15. **GUINEE JF.** Epidemiologic approach to cancer. In: Becker FF, ed. Cancer 1. 2nd ed. New York and London: Plenum Press, 1982: 201-228.
16. **ANDERSON DE.** Cancer eye in cattle. Mod Vet Pract 1970; 51: 43-47.
17. **MONLUX AW, ANDERSON WA, DAVIS CL.** The diagnosis of squamous cell carcinoma of the eye (cancer eye) in cattle. Am J Vet Res 1957; 18: 5-34.
18. **BLACKWELL RL, ANDERSON DE, KNOX JH.** Age incidence and heritability of cancer eye in Hereford cattle. J Anim Sci 1956; 15: 943-951.
19. **ROUBICEK CB, RAY DE.** Genetic study of "cancer eye" in Hereford cows. Proc Am Soc Anim Sci 1974; 25: 49-51.
20. **IVASCU I.** Occurrence of bovine eye neoplasms in some abattoirs and veterinary clinics in Transylvania. Wien Tierarztl Monatschr 1971; 58: 336-339.
21. **NAIR CKP, SASTRY GA.** A survey of animal neoplasms in Madras State. I. Bovine. Indian Vet J 1954; 30: 325-331.
22. **COCK EV.** Some clinical observations on *Thelazia rhodessi* and squamous cell carcinoma in bovine eyes. Rhod Vet J 1972; 2: 62-63.
23. **EPSTEIN B.** Isolation of bovine rhinotra-

cheitis virus from ocular squamous cell carcinomas of cattle. Revista de Medicina Veterinaria 1972; 53: 105-110.
24. **ROUBICEK CB, SWINGLE RS, RAY DE.** Genetics of cancer eye in beef cattle. J Ariz Acad Sci 1975; 10: 31.
25. **ROTH JA, KAEBERLE ML.** Effect of glucocorticoids on the bovine immune system. J Am Vet Med Assoc 1982; 180: 894-901.
26. **CLEAVER JE, KAINER RA, ZELLE MR.** Ocular squamous cell carcinoma (cancer eye) in Hereford cattle: radiation repair processes and a comparison of cultured cells with xeroderma pigmentosum in man. Am J Vet Res 1979; 33: 1131-1136.
27. **JENNINGS PA, LAVIN MF, HUGHES DJ, SPRADBROW PB.** Bovine ocular squamous cell carcinoma: lymphocyte response to phytohaemagglutinin and tumor antigen. Br J Cancer 1979; 40: 608-614.
28. **LINDSAY GC, HECK FC, ENGLAND RB.** Ocular squamous cell carcinoma: immunological responses to tumor tissue and phytomitogens. Res Vet Sci 1978; 24: 113-117.
29. **JENNINGS PA, HUGHES DJ, LAVIN ML.** An animal model relating UV sensitivity and reduced DNA repair to increased incidence of carcinoma. Proc Aust Biochem Soc 1979; 12: 81.
30. **ANDERSON DE, POPE LS, STEPHENS D.** Nutrition and eye cancer in cattle. J Natl Cancer Inst 1979; 45: 697-707.
31. **ANDERSON DE, LUSH JL, CHAMBERS D.** Studies on bovine ocular squamous carcinoma ('cancer eye'). II. Relationship between eyelid pigmentation and occurrence of cancer eye lesions. J Anim Sci 1977; 16: 739-746.
32. **CLARK RT, BRINKS JS, BOGART R, HOLLAND LA, ROUBICEK CB, PAHRISH OF, BENNETT JA, CHRISTIAN RE.** Beef cattle breeding research in the western region. Oregon State Univ Agric Exp Sta., Tech Bull 1963; 73: 1-72.
33. **VOGT DW, ANDERSON DE.** Studies on bovine ocular squamous cell carcinoma "cancer eye". XV. Heritability of susceptibility. J Hered 1964; 55: 133-135.
34. **KOPECKY KE, PUGH GW JR, HUGHES DE, BOOTH GD, CHEVILLE NF.** Biological effect of ultraviolet radiation on cattle: bovine ocular squamous cell carcinoma. Am J Vet Res 1979; 40: 1783-1788.
35. **DMOCHOWSKI L.** Electron microscope studies of the replication of a virus isolated from bovine cancer eye lesions. Proc Am Assoc Cancer Res 1967; 8: 14.
36. **FORD JN, JENNINGS PA, SPRADBROW PB, FRANCIS J.** Evidence for papillomaviruses in ocular lesions in cattle. Res Vet Sci 1982; 32: 257-259.
37. **SYKES JA, DMOCHOWSKI L, STATEN W, RUSSELL WO.** Bovine ocular squamous cell carcinoma. IV. Tissue culture studies of bovine ocular squamous cell carcinoma and its benign precursor lesions. J Natl Cancer Inst 1961; 26: 445-471.
38. **TAYLOR RL, HANKS MA.** Viral isolations from bovine eye tumors. Am J Vet Res 1969; 30: 1885-1886.
39. **ANDERSON DE.** Effects of pigment on bovine ocular squamous cell carcinoma. Ann NY Acad Sci 1963; 100: 436-446.
40. **TAYLOR RL, KANKS MA.** Developmental changes in precursor lesions of bovine ocular carcinoma. Vet Med Small Anim Clin 1972; 67: 669-671.
41. **EPSTEIN WL, FUKUYAMA K, EPSTEIN JH.** UV light, DNA repair and skin carcinogenesis in man. Fed Proc 1971; 30: 1766-1771.
42. **SCHACTER B, LEDERMAN MM, LEVINE MS, ELLNER JJ.** Ultraviolet radiation inhibits natural killer activity and lymphocyte proliferation. J Immunol 1983; 130: 2484-2487.
43. **SPELLMAN CW, DAYNES RA.** Ultraviolet light, tumors and suppressor T cells. Hum Pathol 1981; 12: 299-301.
44. **JENSEN PJ.** The involvement of antigen-presenting cells and suppressor cells in the ultraviolet radiation induced inhibition of secondary cytotoxic-T cell sensitization. J Immunol 1983; 130: 2071-2074.
45. **BURNS JC, MURRAY BK.** Conversion of herpetic lesions to malignancy by ultraviolet exposure and promoter application. J Gen Virol 1981; 55: 305-313.
46. **LADOUCEUR CA, KAZACOS KR.** Eye worms in cattle in Indiana. J Am Vet Med Assoc 1981; 178: 385-387.
47. **BOLLAG W.** Vitamin A and retinoids: from nutrition to pharmacotherapy in dermatology and oncology. Lancet 1983; 5: 860-863.
48. **HOD I, PERK K.** Intranuclear microspherules in bovine ocular squamous cell carcinoma. Refuah Vet 1973; 30: 41-44.
49. **SCOTTISH VETERINARY INSPECTION SERVICE REPORT.** Eye lesions associated with infectious bovine rhinotracheitis virus infection. Vet Rec 1983; 4: 398.
50. **ANSON MA, BENFIELD DA, McADARAGH JP.** Bovine herpesvirus-5 (DN-599) antigens in cells derived from bovine ocular squamous cell carcinoma. Can J Comp Med 1982; 46: 334-337.
51. **HOMAN EJ, EASTERDAY BC.** Further studies on naturally occurring latent bovine herpesvirus infection. Am J Vet Res 1981; 42: 1811-1813.