Retrospective study of tumors from cattle slaughtered in Lombardy (Italy): preliminary evaluation on the establishment of a bovine cancer registry

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Veterinaria Italiana 2022, **xx** (x), xxx-xxx. doi: 10.12834/VetIt.2421.15367.1
Accepted: 14.06.2021 | Available on line: xx.xx.2022

Keywords
Abattoirs,
Cattle,
Comparative oncology,
Neoplasms,
Registries,
Risk factors.

Summary
Forty-one tumors were detected in a population of 1,649,003 cattle slaughtered in 4 abattoirs in Lombardy over a 5-year period, for an overall prevalence of 2.5 tumors per 100,000 cattle. Tumors were classified according to the WHO histological classification of tumors of domestic animals. Alimentary and hemopoietic systems were commonly affected with 9 cases each. Other affected sites were the respiratory (n = 3), urinary (n = 2), endocrine (n = 2), musculoskeletal (n = 2), nervous (n = 1), and cardiovascular (n = 1) systems. The peritoneum was affected by 6 cases, while the primary location of 3 tumors of the connective tissues and 3 metastatic carcinomas was unidentified. Liver tumors and mesotheliomas, for which environmental risk factors are well-known in humans, were common, as well as tumors typically encountered in pediatric human patients (tumors of mesenchymal tissues, pulmonary blastomas and nephroblastomas). These findings suggest the useful role of bovines as sentinel and model for human carcinogenesis. Our study indicates that the establishment of a bovine cancer registry in Lombardy is feasible considering its potential contribution to understanding the role of environmental risk factors in the genesis of tumors in animals and humans.

Introduction

Epidemiological studies are important in defining the occurrence of different types of tumors within a population. The comparison of cancer epidemiology and biology between humans and animals is a valuable process able to provide new insights in known risk factors and to identify unknown ones.

Compared to companion animals, tumors in cattle are infrequently diagnosed, given the short lifespan and the limited diagnostic workup pursued in this species. This is likely the reason for the lack of systematic studies on tumor incidence in a defined bovine population. The literature reporting tumors in the bovine species is scanty and outdated. Veterinary pathological studies report the presence of tumors in a percentage that varies between 8.74% and 14% in cattle specimens submitted for

Please refer to the forthcoming article as: Cappelleri A. et al. 2022. Retrospective study of tumors from cattle slaughtered in Lombardy (Italy): preliminary evaluation on the establishment of a bovine cancer registry. Vet Ital. doi: 10.12834/VetIt.2421.15367.1.

investigation of selected lesions (Alvarez *et al.* 1982, Lucena *et al.* 2011, Marosfoi *et al.* 2008, Murray 1968, Naghshineh *et al.* 1991). The prevalence of tumors is extremely low and variable in surveys conducted in slaughtered cattle, ranging from 23 per 100,000 to 227 per 100,000 cattle (Anderson *et al.* 1969, Brandly and Migaki 1963, Misdorp 1967, Reisinger 1963). The most commonly reported tumors are lymphoma and ocular squamous cell carcinoma (Anderson *et al.* 1969, Bastianello 1982, Brandly and Migaki 1963, Cotchin 1960, Dukes *et al.* 1982, Monlux *et al.* 1956, Murray 1968, Naghshineh *et al.* 1991, Plummer 1956, Priester and Mantel 1971, Reisinger 1963, Russell *et al.* 1956, Sastry and Twiehaus 1964, Shortridge and Cordes 1971). Tumors of the adrenal glands and schwannomas are also quite common (Bundza *et al.* 1986, Hamir *et al.* 1985, Misdorp 1967, Monlux *et al.* 1956, Wright and Conner 1968).

Cancer registries are permanent structures aimed to record continuously and systematically all tumor cases occurring in a defined population, along with clinical and pathological characteristics of the tumors (Jensen 1991). These represent primary tools to monitor the epidemiological evolution of different types of tumors and to study the associated risk factors, with the ultimate goal of planning diagnostic, therapeutic and prophylactic interventions (Jensen 1991). The first known cancer registry for human patients was the Danish Cancer Registry established in 1942 (Storm *et al.* 1997) and, from then on, cancer registries went through a notable development. On the contrary, only few veterinary cancer registries have been established so far, with the firsts being introduced in the 1960s (Brønden *et al.* 2007). One of the largest and best known is the California Animal Neoplasm Registry (CANR), that was established in 1963 and recorded more than 30,000 malignant tumors from both companion and livestock animals over a 3-year period (Dorn *et al.* 1968).

In Italy, the first veterinary cancer registry was the Animal Tumor Registry of Genoa established in 1985 by the Istituto Zooprofilattico Sperimentale del Piemonte, Liguria e Valle d'Aosta (Merlo *et al.* 2008). In the last 20 years several Italian regions have started new animal cancer registries. It is the case of Piedmont (2001), Sicily (2003), Veneto (2005), Tuscany (2006), Campania (2010), Lazio (2010), Emilia Romagna (2012), Umbria (2014), Sardinia (2014) and Marche (2016). However, these registries have been largely focused on the collection of tumors of small animals (Baioni *et al.* 2017, Manuali *et al.* 2019, Merlo *et al.* 2008, Vascellari *et al.* 2009). Given their nature of livestock animals, we believe that bovines might function as useful "sentinels" for detecting environmental risk factors possibly involved in animal and human carcinogenesis.

Our study had two major objectives: 1) define the overall prevalence of different types of tumors in cattle slaughtered in Lombardy (Italy); 2) collect data on slaughtered cattle that could be compared to a specific bovine population in Lombardy. These will allow to evaluate the feasibility and the potential of the establishment of a bovine cancer registry in Lombardy. To our knowledge, this is the first Italian work studying the prevalence of tumors in slaughtered cattle.

Materials and methods

Sample collection

In the period 2012-2016, all suspected tumoral lesions found in cattle slaughtered in 4 abattoirs located in Lombardy (Italy) were sampled and submitted to the Histopathology Laboratory of the Istituto Zooprofilattico Sperimentale della Lombardia e dell'Emilia Romagna. At the abattoir, each specimen was fixed in 10% neutral buffered formalin and sent to the laboratory along with identification data of the affected animal and gross description of the lesion provided by the official veterinarians.

Histopathology, histochemistry and immunohistochemistry

Formalin-fixed samples were routinely processed for histology, embedded in paraffin, sectioned at 4 µm and stained with hematoxylin and eosin. To confirm the diagnosis, in some cases further histochemical stains (Alcian Blue and Periodic Acid-Schiff) and/or immunohistochemistry using the indirect peroxidase-based detection method were performed. For immunohistochemistry, dewaxing of tissue sections and antigen retrieval were performed using the Dewax and HIER Buffer H pH 9 (Thermo Fisher Scientific, Freemont, CA, USA) at boiling temperature for 40 min. Endogenous peroxidase was blocked with 3% H_2O_2 for 10 min at room temperature. Nonspecific protein binding was blocked with 10% normal goat or horse serum for 30 min or with Novocastra Protein Block™ (Leica Biosystems, Nussloch, Germany) for 5 min at room temperature. The slides were then incubated for 1 hour at room temperature with the following primary antibodies: mouse monoclonal anti-smooth muscle actin (SMA) 1:1,000 (clone 1A4, Dako, Glostrup, Denmark), rabbit polyclonal anti-glial fibrillary acidic protein (GFAP) 1:10,000 (Dako, Glostrup, Denmark), rabbit polyclonal anti-CD3 1:300 (Dako, Glostrup, Denmark), rabbit polyclonal anti-CD20 1:250 (Thermo Fisher Scientific, Freemont, CA, USA), mouse monoclonal anti-cytokeratin 1:250 (clone AE1/AE3, Dako, Glostrup, Denmark), rabbit

Veterinaria Italiana 2022, **xx** (x), xxx-xxx. doi: 10.12834/VetIt.2421.15367.1

polyclonal anti-chromogranin A 1:400 (Dako, Glostrup, Denmark), rabbit monoclonal anti-desmin 1:600 (clone Y66, Abcam, Cambridge, UK), rabbit polyclonal anti-S100 1:3,000 (Dako, Glostrup, Denmark), mouse monoclonal anti-vimentin 1:1,000 (clone 3B4, Dako, Glostrup, Denmark), rabbit polyclonal anti-von Willebrand factor (vWF) 1:2,000 (Dako, Glostrup, Denmark), rabbit monoclonal anti-Wilm's tumor protein (WT-1) 1:200 (clone CAN-R9(IHC)-56-2, Abcam, Cambridge, UK). Biotinylated secondary antibodies 1:200 (Vector Laboratories, Burlingame, CA, USA) were added for 30 min. The Vectastain® Elite ABC-Peroxidase kit (Vector Laboratories, Burlingame, CA, USA) was applied in accordance with the manufacturer's instructions. The immunoreaction was observed with the Peroxidase ImmPACT® DAB Substrate (Vector Laboratories, Burlingame, CA, USA). Alternatively, the Novolink™ Max Polymer Detection System (Leica Biosystems, Nussloch, Germany) was applied and the immunoreaction was observed with the NovaRED® Peroxidase Substrate Kit (Vector Laboratories, Burlingame, CA, USA). Sections were counterstained with Mayer's hematoxylin. Known positive controls were included in each immunolabeling assay.

Inclusion criteria

Only tumor cases confirmed by histology were included in the study. Based on histopathological findings and on histochemistry and/or immunohistochemistry when applied, each tumor was classified according to the World Health Organization (WHO) histological classification of tumors of domestic animals (Beveridge and Sobin 1974).

Abattoirs and population data

Data regarding number and origin of cattle slaughtered in Italy in the period of study were provided by the Italian Database for Zootechnical livestock Registration (IDZR) established by the Italian Ministry of Health.

The cases included in the study were collected in 4 different abattoirs, one located in the province of Lodi (abattoir #1) and three in the province of Mantua (abattoirs #2, #3, #4). The total number of cattle slaughtered per year in each abattoir in the period 2012-2016 was provided by the official veterinarians, sorted out by origin (province and region) of the animals. Data regarding age and sex of slaughtered animals were limited to 2 categories: 'cows older than 2 years' and 'others'.

Regarding cattle with tumors, data on age, sex, breed and origin of the animals were collected from the Veterinary Information System of the Italian Ministry of Health, based on the animals' individual identification codes provided with the samples.

Results

Study population

From 2012 and 2016, an overall number of 1,649,003 cattle was slaughtered in the 4 abattoirs selected in this study. Of these, 776,457 (47%) were slaughtered in the abattoir #1 and 872,546 (53%) in the other 3 abattoirs. Fifty-four percent of all cattle (n = 892,670) were from farms located in Lombardy. Of these, 475,340 were slaughtered in the abattoir #1 and 417,330 in the abattoirs #2, #3, #4. The remaining cattle (n = 756,333) were from other regions. Considering the data referring to the 2012-2016 period, 12.9% of the total number of cattle from Lombardy slaughtered in Italy were slaughtered in the abattoir #1 and 11.4% in the #2, #3 and #4. Therefore, between 2012 and 2016, the abattoirs selected in this study slaughtered 24.3% of the total cattle reared in Lombardy.

Tumor prevalence

Forty-one tumors were collected, 14 (34%) from cattle slaughtered in the abattoir #1 and 27 (66%) in the abattoirs #2, #3 and #4. The overall prevalence of tumors was 2.5 per 100,000 cattle. The prevalence of tumors found in the abattoir #1 was 1.8 per 100,000 cattle, while the abattoirs #2, #3 and #4 reported a prevalence of 3.1 tumors per 100,000 cattle. All tumors where from cattle born and raised in Italy, except for 2 animals that were born in France and raised in Italy. Considering cattle coming from farms located in Lombardy only, 20 tumors were collected, accounting for a prevalence of 2.2 per 100,000 cattle.

Twenty-six cattle (63%) included in the study were ≥ 5 years old, 13 cattle (32%) between 2 and 5 years and 2 cattle (4.9%) were under 2 years of age. Two cattle were males (approximately 2 years of age), all the others were adult cows except one which was a younger female. The Holstein Friesian breed was overrepresented, accounting for 63.4% (26 cattle) of all cases. The breed of 4 cattle was unknown.

Types of tumors

Distribution of the 41 tumors according to anatomical location and age group of the animals is reported in Table I. Tumors of mesenchymal tissues were the most common with 12 (29.3%) cases affecting different sites (heart, forelimb, foot and others). Among these, 11/12 were malignant. Five malignant mesotheliomas of the peritoneum

Table I. *Distribution of tumors in cattle according to anatomical location and age group.*

System	Age groups (years)					Number of cases (%)
	1 - 2	**2 - 3**	**3 - 5**	**5 - 8**	**≥ 8**	
Alimentary		1		3	5	9 (22%)
Hematopoietic	1	2	4	2		9 (22%)
Endocrine				1	1	2 (4.9%)
Nervous					1	1 (2.4%)
Respiratory		2		1		3 (7.3%)
Urinary	1				1	2 (4.9%)
Cardiovascular					1	1 (2.4%)
Musculoskeletal				1	1	2 (4.9%)
Other		3	1	2	6	12 (29.3%)
Total	2 (4.9%)	8 (19.5%)	5 (12.2%)	10 (24.4%)	16 (39%)	41

were found and classified as epithelioid (1), biphasic (2) and fibrous (2), based on histochemical and immunohistochemical results (Figure 1). The youngest cattle with tumors of mesenchymal tissues were between 2 and 5 years of age, and were

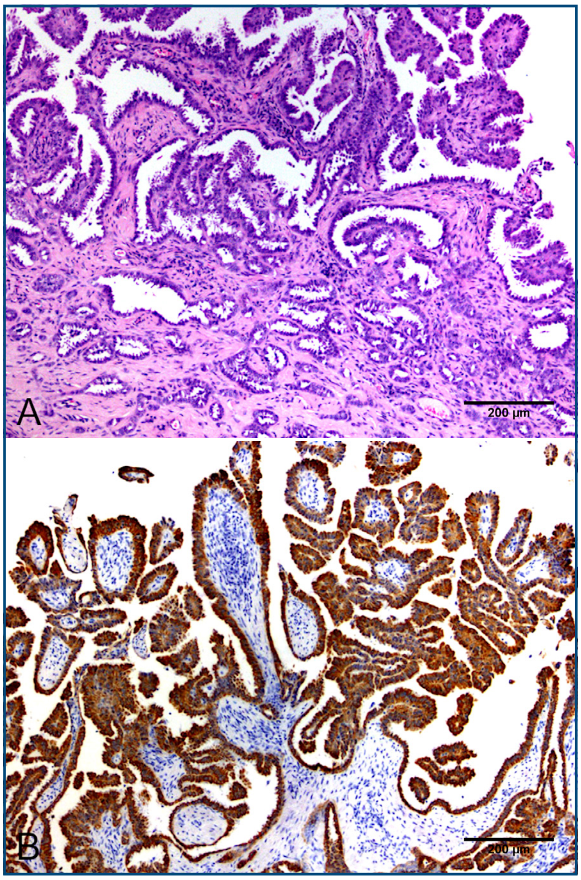

Figure 1. *Epithelioid mesothelioma of the bovine peritoneum.* **A.** Numerous branching outgrowths of mesothelial neoplastic cells supported by a central core of stroma give the tumor the typical papillary pattern. H&E, original magnification 100x. **B.** Immunolabeling for pan-cytokeratin shows an intense signal in neoplastic epithelial-like cells lining the papillae. Note the marked anisocytosis of the mesothelial cells positive to the marker. Immunohistochemistry for pan-cytokeratin with DAB chromogen, original magnification 100x.

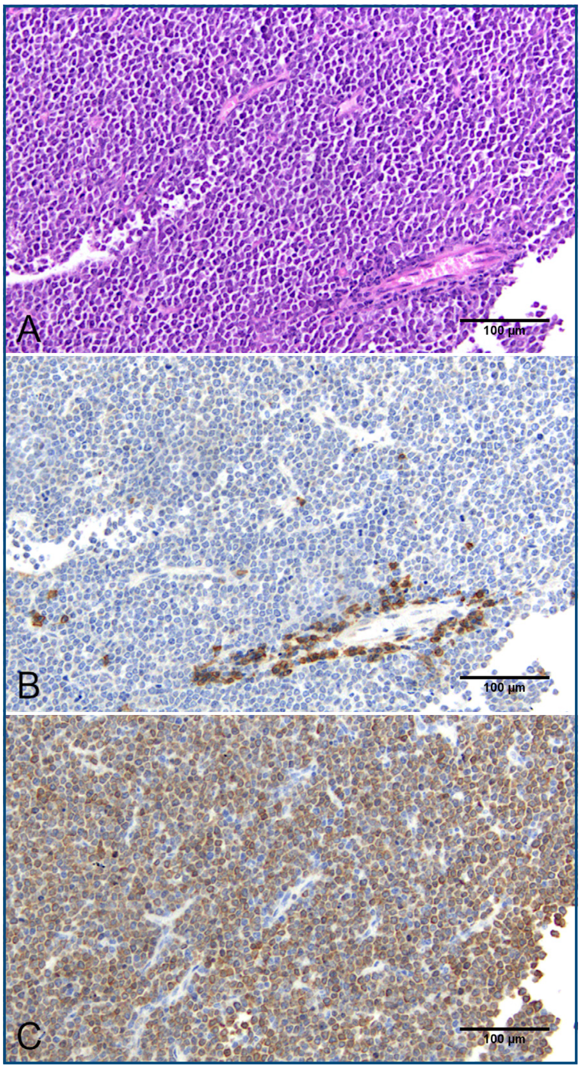

Figure 2. *T-cell lymphoma of the bovine lymph node.* **A.** The organ is effaced by a sheet of densely packed round neoplastic cells. H&E, original magnification 200x. **B.** Same field as A. Immunolabeling for CD20 shows few positive normal B lymphocytes in the perivascular space. Immunohistochemistry for CD20 with DAB chromogen, original magnification 200x. **C.** Same field as A and B. Immunolabeling for CD3 confirms the T-cell phenotype of neoplastic lymphocytes. Immunohistochemistry for CD3 with DAB chromogen, original magnification 200x.

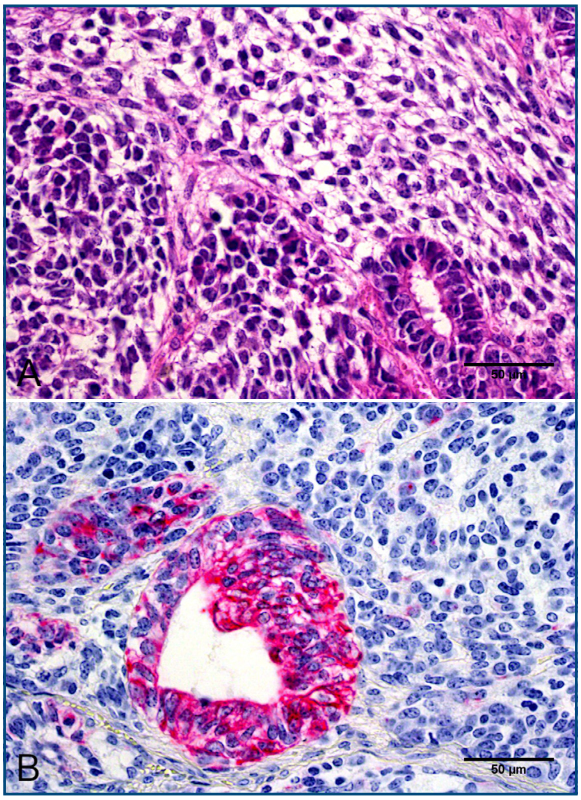

Figure 3. *Nephroblastoma in bovine.* **A.** The three typical components of nephroblastoma are shown: embryonal epithelium forming a fairly well-developed tubule (lower right), undifferentiated blastema, and myxomatous mesenchyme. H&E, original magnification 400x. **B.** Immunolabeling for pan-cytokeratin is detectable in the epithelial cells that form a tubule-like structure. Immunohistochemistry for pan-cytokeratin with NovaRED® chromogen, original magnification 400x.

affected by fibrosarcoma (2 cases), myxosarcoma (1 case), and mesothelioma (1 case). Tumors of the alimentary system were seen in 9 cases (22%), and all of them were tumors of the liver, which also was the most commonly affected organ in this study. These included 5 hepatocellular adenomas and 4 malignancies (2 hepatocellular carcinomas and 2 cholangiocarcinomas). The hematopoietic system was affected by 9 lymphomas (22%), also the most common type of tumor. All lymphomas but one were immunoreactive to CD3 and thus classified as T-cell lymphomas (Figure 2). The remaining one reacted to CD20 and thus was classified as B-cell lymphoma. Other tumors were found in the respiratory system (3; 7.3%), endocrine and urinary (2 tumors each). Among these, 2 pulmonary blastomas, and 1 nephroblastoma were found in cattle under 3 years of age (Figure 3). Only 1 tumor affecting the peripheral nervous system (schwannoma) was found in a 12-year-old cow. In Table II details on primary sites and types of tumors are reported.

Ten of the tumors were metastatic (Table III); it was not possible to determine the primary location of 3 carcinomas that had metastasized to the peritoneum.

Discussion

Study population and tumor prevalence

In the study period, 24.3% of the overall population

Table II. *Primary sites and types of tumor detected in cattle according to the WHO histological classification of tumors of domestic animals.*

System	Organ / Site	Type	Number of cases (%)
Alimentary	Liver	Hepatocellular adenoma	5 (12.2%)
		Hepatocellular carcinoma	2 (4.9%)
		Cholangiocarcinoma	2 (4.9%)
Hematopoietic	Lymph node (4); Thymus (2); other (3)	Lymphoma	9 (22%)
Endocrine	Adrenal gland	Adrenal cortical carcinoma	2 (4.9%)
Nervous	Pheripheral nerve	Schwannoma	1 (2.4%)
Respiratory	Lung	Pulmonary blastoma	2 (4.9%)
		Bronchioloalveolar carcinoma	1 (2.4%)
Urinary	Kidney	Nephroblastoma	1 (2.4%)
		Undifferentiated carcinoma	1 (2.4%)
Cardiovascular	Heart	Fibroma	1 (2.4%)
Musculoskeletal	Forelimb	Rhabdomyosarcoma	1 (2.4%)
	Foot	Fibrosarcoma	1 (2.4%)
Other	Peritoneum	Mesothelioma	5 (12.2%)
		Fibrosarcoma	1 (2.4%)
	n.d.*	Fibrosarcoma	2 (4.9%)
	n.d.*	Myxosarcoma	1 (2.4%)
	n.d.*	Carcinoma	3 (7.3%)
Total			41

*n.d. = not determined

Table III. *Metastatic tumors in cattle.*

Primary tumor	Location of metastases
Bronchioloalveolar carcinoma	Lymph nodes
Pulmonary blastoma	Peritoneum
Undifferentiated renal carcinoma	Lymph nodes, lung, liver
Cholangiocarcinoma	Lymph nodes
Peritoneal fibrosarcoma	Lymph nodes
Peritoneal mesothelioma	Lymph nodes
Rhabdomyosarcoma of the forelimb	Lymph nodes, lung
Carcinoma of undetermined primary site (3)	Peritoneum

of cattle reared in Lombardy and sent to slaughter in Italy were examined: considering the few abattoirs participating in the study, this is an outstanding percentage.

There is general lack of studies providing prevalence of tumors in slaughtered cattle, and the majority is outdated. Among these, the reported prevalence ranges from 23 to 227 per 100,000 cattle (Anderson *et al.* 1969, Brandly and Migaki 1963, Misdorp 1967, Reisinger 1963). This variability is likely related to the diagnostic method used (gross diagnosis vs histological confirmation). In our study, lesions were sampled during routine post mortem inspection at slaughter, which notably tends to neglect the examination of some organs (for instance the brain). This factor may account for a lower prevalence in our work compared to others.

The prevalence of tumors was calculated by merging data provided by the abattoirs participating in the study with information in the Italian Database for Zootechnical livestock Registration (IDZR). The IDZR is a pivotal tool for the monitoring of the bovine population on a national level. Data on the number of cattle present in every region of Italy are accessible to the public and updated regularly. Data are broken down by age, sex, breed and category of the animals (meat or milk production). Furthermore, the IDZR reports the number of cattle that are slaughtered in a specific region, which region these animals are from, along with information on sex, age and category of the animals. However, standardization and consistency in processing and presenting data are required across different abattoirs to establish a reliable epidemiological surveillance platform such as a cancer registry.

Types of tumors

In our study, the prevalence of mesotheliomas (12.2%) was high if compared to that found in the literature, where the highest value was 6.5% of all tumors (Plummer 1956). Mesotheliomas can be congenital or can develop in older cattle (Munday *et al.* 2016). In our study, all the affected animals were adults.

Tumors of the liver were common (22%); this relative high prevalence is likely explained by the thorough examination of the liver at post mortem inspection. While others reported metastatic tumors to be more prevalent in the liver (Anderson and Sandison 1968), only 1 metastatic tumor was observed in our study.

Lymphoma showed a prevalence (22%) similar to that reported in literature, with the sporadic form being prevalent if not exclusive (Anderson *et al.* 1969, Cotchin 1960, Naghshineh *et al.* 1991, Shortridge and Cordes 1971). The immunophenotype of lymphomas, together with the young age of affected animals, supported the diagnosis of sporadic lymphoma.

Adrenal tumors and schwannoma are reported to be quite common in cattle (Bundza *et al.* 1986, Hamir *et al.* 1985, Misdorp 1967, Monlux *et al.* 1956, Wright and Conner 1968). Adrenal tumors in our study (4.9%) were adrenal cortical carcinomas, one of the most common type of tumor in this site (Grossi *et al.* 2013). Only 1 schwannoma was found, accounting for a lower prevalence if compared to other studies (Hamir *et al.* 1985, Misdorp 1967, Monlux *et al.* 1956).

Of particular interest in our study was the collection of some tumors that are usually reported in children, like pulmonary blastoma and nephroblastoma. Pulmonary blastoma is very rare both in animals and humans. Only four cases have been reported in the bovine species so far (Carminato *et al.* 2008, Kelley *et al.* 1994). Nephroblastoma is common in young animals, especially pigs and chickens, but it is considered to be rare in cattle (Yamamoto *et al.* 2006).

Metastasizing carcinomas of unidentified origin represented 7.3% of all tumors, and all involved the peritoneum. This finding is not uncommon in studies carried out at slaughter (Dukes *et al.* 1982, Lucena *et al.* 2011, Plummer 1956), according to which the peritoneal involvement might be ascribed to uterine or ovarian carcinomas (Monlux *et al.* 1956).

Cattle as model of cancer

Dogs and cats are considered useful models in the study of human cancer since they share the same environment and some habits with humans, being hence exposed to the same risk factors involved in the genesis of tumors (Brønden *et al.* 2007, Misdorp 1996). However, for this reason pets are subject to the same bias factors (for instance passive smoke) which could mask the effective role of environmental risk factors. On the contrary, the bovine population represents a useful 'sentinel' for detecting environmental risk factors and studying their role in carcinogenesis, excluding the confounding factors commonly encountered in companion animals. Another advantage of cattle is that, given their short lifespan, cattle represent the ideal population to study tumors that are typical of pediatric age in humans, such as soft tissue sarcomas, pulmonary blastomas and nephroblastomas, all types encountered in our survey (Abbo *et al.* 2018, Parham 2018).

As previously reported, studies of cancers in wildlife have shown intimate association between cancer and environmental contamination (Thompson and Anthony 2005). The easier availability of tumor cases in livestock rather than wild animals, makes cattle valuable biological indicators of carcinogenic pollutants in specific areas. In support to this thesis, an Italian work suggested the role of sheep as bio-indicators in the evaluation of environmental diffusion of asbestiform fibers in a volcanic area of Sicily, where a high risk of pleural mesothelioma in humans was found in the absence of occupational exposure (DeNardo *et al.* 2004).

Accordingly, the bovine species could play the role of 'sentinel' for human tumors induced by exposure to environmental carcinogens. Concerning liver tumors, for example, which were particularly common in our study, aflatoxin B1 is a well-known hepatic carcinogen in humans and appears to have the same role in animals, including cattle (Adamesteanu *et al.* 1974, Newberne and Rogers 1973, Sinnhuber *et al.* 1977). Since cattle are exposed primarily and more heavily than humans to the toxin present in the feed, these animals can be considered an interesting model to better understand the role of aflatoxin B1 in human hepatocarcinogenesis. Similarly, bovine mesothelioma, which was quite common in our study, can be regarded as an interesting comparative model for the human counterpart. The exposition to asbestos fibers is considered the major risk factor in the genesis of this type of tumor in humans (Dragon *et al.* 2015). Ruling out the occupational hazard which is human prerogative, the real carcinogenic role of asbestos fibers of environmental origin such as those shed by rooftops of buildings or animal facilities is still not clear. For this reason, cattle that dwell in asbestos-containing farms should be considered an important object of study.

Conclusions

The present study demonstrated the feasibility and the potential value of the establishment of a bovine cancer registry. The bovine species offers three main advantages: 1) considering that every slaughtered animal undergoes a complete post mortem examination by a veterinarian, a thorough survey can be easily performed without sensitive increase of time or personnel; 2) being the prevalence of tumors in cattle quite low, expenses for laboratory investigations (histology and immunohistochemistry) are minimal; 3) since identification of cattle is mandatory by law and all the data are recorded in accessible databases, characteristics of the studied population, including overall number, sex, age and breed of the animals, are known. On the contrary, several studies reported the inaccuracy of the estimated canine population, since not all the owners comply with the reporting of new births/acquisitions and deaths of their pets (Baioni *et al.* 2017, Merlo *et al.* 2008, Vascellari *et al.* 2009).

There is evidence that many cancer registries of animals were established worldwide (Brønden *et al.* 2010, Grüntzig *et al.* 2015, Tedardi *et al.* 2015). Most of them, however, have had or still have a range of action limited to dogs and cats. Bovine cancer registries could represent a step forward to understand the role that etiological and risk factors play in the genesis of tumors in animals, with the fundamental perspective of a comparative approach with humans.

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