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Cancer Incidence in Pet Dogs: Findings of the Animal Tumor Registry of Genoa, Italy

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Background: The occurrence of spontaneous tumors in pet animals has been estimated in a few European and North American veterinary cancer registries with dissimilar methodologies and variable reference populations.

Objectives: The Animal Tumor Registry (ATR) of Genoa, Italy, was established in 1985 with the aim of estimating the occurrence of spontaneous tumors in dogs.

Methods: Six thousand seven hundred and forty-three tumor biopsy specimens were received from local veterinarians in the Municipality of Genoa between 1985 and 2002. Three thousand and three hundred and three (48.9%) biopsy specimen samples were diagnosed as cancer and were coded according to the International Statistical Classification of Diseases (ICD-9).

Results: Mammary cancer was the most frequently diagnosed cancer in female dogs, accounting for 70% of all cancer cases. Incidence of all cancers was 99.3 per 100,000 dog-years (95% CI: 93.6–105.1) in male dogs and 272.1 (95% CI: 260.7–283.6) in female dogs. The highest incidence rates were detected for mammary cancer (IR = 191.8, 95% CI: 182.2–201.4) and for non-Hodgkin's lymphoma (IR = 22.9, 95% CI: 19.7–26.5) in bitches and for non-Hodgkin's lymphoma (IR = 19.9, 95% CI: 17.4–22.7) and skin cancer (IR = 19.1, 95% CI: 16.6–21.8) in male dogs. All cancer IR increased with age ranging between 23.7 (95% CI: 18.4–30.1) and 763.2 (95% CI: 700.4–830.1) in bitches and between 16.5 (95% CI: 12.8–21.1) and 237.6 (95% CI: 209.1–269.0) in male dogs aged $\leq$3 years and $>$9–11 years.

Conclusion: This study summarizes the work done by the ATR of Genoa, Italy, between 1985 and 2002. All cancer incidence was 3 times higher in female than in male dogs, a difference explained by the high rate of mammary cancer observed in bitches. Because a biopsy specimen was required to make a cancer diagnosis, cancer rates for internal organs cancers, such as respiratory and digestive tract cancers may have been underestimated in the study population.

Key words: Age; Breed; Cancer registry; Canine incidence rates.

The 1st documented attempt to compute reliable statistics on cancer occurrence in humans took place in Germany in 1900.[1] Some 30 years later, the 1st registration of cancer patients in the hospitals of Hamburg was systematically carried out and data were centralized at the City Public Health Department to form the basis of the Hamburg Cancer Registry.[2] For the past 50 years, human cancer incidence data have been regularly published by the International Agency for Research on Cancer in its well-known publication series Cancer Incidence in Five Continents, the most recently published report referring to more than 200 human populations for the years 1993–1997.[3] Attempts at establishing a cancer registration system for pets are much more recent (early 1960s) and include the California Animal Neoplasm Registry (ANR)[4] and the USA Veterinary Medical Data Program (VMDP).[5] The Tulsa Registry of Canine and Feline Neoplasms,[6] the Animal Tumor Registry of Genoa (ATR),[7] and the Southern Ontario Registry[8] were established during the 1970s and 1980s in United States, Italy, and Canada, respectively. In the early 1990s, the Sweden Insured Dogs Registry[9] was launched, and in 1997 the UK Insured Dogs was established in the United Kingdom.[10] A Canine Cancer Registry was set up in the year 2000 in the Local Health Authority of Ivrea, Italy.[11]

Similar to human cancer registration, estimating cancer incidence among pets requires the enumeration of all new cases of cancer diagnosed in a given population (ie, the population at risk) in a given time interval. Reliable estimates of cancer incidence require valid data on the demographics of the registry population and a complete enumeration of the cancer cases diagnosed in that population. The incomplete ascertainment of the cases and of the population at risk inevitably will result in biased estimates of the true incidence rate (IR). Human cancer registries rely on complete demographic data to identify the population at risk and on standardized procedures to identify all incident cancer cases, classify them according to diagnostic procedures, and code them according to the International Classification of Diseases, Injuries, and Causes of Death.[12] Complete demographic registries are not available for pets, and early epidemiologic studies reporting canine cancer occurrence were based on the data gathered by veterinary teaching hospitals,[13,14] with a few studies attempting to estimate population-based cancer IRs.[5,7,8,10,11] The difficulties encountered in the computation of reliable cancer IRs in companion animals were handled differently by each animal cancer registry.[5,7,8,10,11] The population at risk was defined as all insured dogs in the United Kingdom,[10] the dogs owned by the residents of the Alameda and Contra Costa Counties, CA, USA (estimated by a probability sample survey of households),[4] the registered dog population of

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Table 1. Tumor incidence rates (all sites) estimated in pet dogs by country and tumor characteristics.

Country	Years	Canine Population		Tumors	Incidence Rate[b]	Ref.#
		Base Population	No.[a]			
UK	1997–1998	UK insured dogs[c]	130,684	Cancers[d]	747.9	(11)
				All neoplasia related claims[d]	1,948	
California USA	1963–1966	Alameda County	1,031	Cancers	381	(5)
				Nonmalignant tumors	1,130	
Ontario Canada	1999	Veterinary Clinics	63,500	Cancers	850	(9)
				All tumors	3,970	
Italy	1985–1994	Genoa County	127,600	Cancers	310	(8)
				Nonmalignant tumors	760	
Italy	2001	Local Health Unit	9,182	Cancers	958.4	(12)

[a]Size of the estimated canine population at risk.
[b]Crude rate defined as the number of cases per 100,000 dogs/year.
[c]All dogs insured with a single UK pet insurance company.
[d]Claims for veterinary treatment identified as being related to neoplasia.

the Genoa County, Italy,[7] and the estimated dog population of the Local Health Authority of Ivrea, Italy.[11] Case ascertainment varied in each specific cancer registration program, including centralized histologic examination of all tumor cases reported by 76 veterinary practices in the Alameda and Contra Costa Counties of California,[4] all tumor-related claims in the United Kingdom,[10] cases diagnosed at private veterinary clinics in Ontario, Canada,[9] tumors reported by local veterinarians in Ivrea, Italy,[11] and those reported to the ATR of Genoa, Italy by approximately 400 Italian veterinary practitioners.[7] Published IRs for approximately all cancers ranged between 310 and 958 per 100,000 dogs (Table 1). Such variation may reflect methodologic differences among registries regarding cancer ascertainment and diagnosis, the use of different nomenclature and classification schemes, different inclusion criteria, and the definition of the population at risk. All of these differences challenge the comparability of the published cancer IRs.[13]

In this study, all tumor cases reported to the ATR of Genoa by the local private veterinary practices between 1985 and 2002 were reviewed, histologically classified, and coded according to the International Statistical Classification of Diseases and Related Health Problems, 9th Revision (ICD-9)[15] and the ICD Oncology 2.[16] Cancers and nonmalignant lesions were used to calculate site, sex, race, and age-specific frequency distributions. The Canine Demographic Registry of the city of Genoa (CDR) was used to estimate the population at risk for the computation of cancer IRs. The city of Genoa is the capital of the Liguria region located in northern Italy and is the 6th largest Italian city with a population of 610,300 in 2001.

Materials and Methods

The ATR of Genoa was established in mid-1985 as a research unit at the National Institute for Research on Cancer of Genoa, Italy. The aims of the ATR were to estimate canine cancer incidence, understand the natural history of cancer occurrence in pet animals, and compare animal and human cancer incidence figures.[7] The ATR unit included histopathology and clinical pathology laboratories. The staff included 3 veterinarians, 1 biologist, a medical doctor, and 4 laboratory technicians. All of the ATR activities were planned in cooperation with the Unit of Epidemiology and Biostatistics of the Institute. The registry closely cooperated with the Institute for Animal Prophylaxis, Unit of Genoa, one of the 10 Italian Public Health Institutes established by the Italian Ministry of Health for animal prophylaxis, food safety, and control. At the time of its launch, Italian veterinarians were informed of the ATR activity and histopathologic diagnosis was offered free of charge. A standardized case-report form specifically designed for the collection of canine and feline cancer cases was available to all veterinarians. They were asked to complete the form (as a requirement for obtaining a histopathologic diagnosis) at the time of excisional surgery and return it to the ATR along with each biopsy. The form's items concerned animal and tumor data, including species, date of birth, breed, sex, ovariohysterectomy or castration status, anatomical site, and date of excision. In 2003, the activity of the ATR was transferred to the Institute for Animal Prophylaxis, Unit of Genoa, which continued cooperation with the Unit of Epidemiology and Biostatistics.

During the period July 1, 1985 to December 31, 2002, the ATR received 40,996 biopsies for histopathologic evaluation from all 21 Italian Regions. They were formalin-fixed, paraffin-embedded, and archived. Trained personnel entered all retrieved data concerning the dogs' demographic characteristics and tumor features (including primary site, histologic diagnosis, and date of diagnosis) in a spreadsheet for consultation and analysis purposes. Thirteen thousand eight hundred twenty-seven biopsy specimens were from animals living in the Liguria Region, 9,927 of which were from the Genoa Municipality; 6,743 biopsies were from dogs, 2,731 from cats, and 913 from other species. Only biopsies from dogs are considered in this paper. Biopsies all were reviewed by expert histopathologists and cancer cases were classified according to their primary site and coded by an expert nosologist according to the ICD-9[15] and the International Classification of Diseases for Oncology 2nd edition (ICDO-2).[16]

Statistical Methods

The demographic registry of the canine population of the city of Genoa (CDR) was obtained from the Local Health Authority 3 where it was established after 1987 National Legislation that required registration of dogs with the Italian Local Health Authorities.[7] The completeness of the CDR remains uncertain because not all owners may report their pet(s) to the Health Authority as required by the law. For this reason, the true population of dogs in the city of Genoa was estimated by the capture-recapture methodology.[17–19] We used the 2-sample capture-recapture model to estimate the unknown size of the canine population by considering the sample of tumor cases collected by the ATR (6,743) and that identified by the CDR (42,108) as being 2 lists constructed from independent sources. The number of dogs recaptured in both samples and those recaptured in just 1 sample were used to compute the total population size by the estimation of the number of dogs not recaptured in either sample.[20,21] To apply this methodology, both the ATR and the CDR electronic data sets were manually inspected and reviewed. The owners' last and first names and addresses, including postal codes and city district codes, and the dogs' dates of birth, breed, and sex were checked for data entry errors. Inconsistencies (eg, the owner's first and last name and address frequently were misspelled or abbreviated; dog breed was misspelled or abbreviated, sex was truncated) and errors (eg, wrong year or month of birth) were systematically corrected using the canine pure breeds list and, for the owners, the Genoa Municipality's demographic data and the official street directory. Dogs were coded as crossbred when the breed reported on the form failed to match the pure breed list. A set of standardized variables was generated and used in the capture-recapture procedure that included the owners' first and last names and complete addresses, and the dogs' dates of birth, breed and sex. Site, age, and sex-specific cancer IRs were computed dividing the number of incident cases coded according to the ICD-9th by the estimated canine population at risk (dog-years of observation) accumulated across the period of observation 1985–2002. The number of dog-years contributed by each dog was defined as the number of years between the date of entry into study (date of birth for dogs born after January 1, 1985) and the date of death or the end of study, whichever event occurred first. IRs were reported for 100,000 dog-years and their 95% CI were calculated on the assumption of a Poisson's distribution of the observed cases. Statistical analysis was performed by Stata Statistical Software.[a]

Results

In all, 6,743 tumor biopsies were reported to the ATR during the first 18 years of activity, of which 3,303 (48.9%) were histologically confirmed cancers and 3,440 (51.1%) were nonmalignant tumors (Table 2). The frequency of biopsy specimens submission across the study period for all biopsies and for hystologically confirmed cancers is shown in Figure 1. The number of biopsies submitted to the ATR increased after the launch of the ATR and since 1988 has remained stable across the study period. The proportion of malignant tumors among the submitted biopsies was constant across the 18 years of activity of the ATR (Fig 1). The capture-recapture estimated average canine population of the Genoa Municipality was 107,981 (63,865 males and 44,116 females) per year (Fig 2). The distribution by age groups and sex (the population pyramid) for 1994 is shown in Figure 2. The canine population contributed to 1,943,725 dog-years of observation across the study period, 794,094 females and 1,149,566 males (Table 2). Dog-years at risk by sex and age group are shown in Table 2. Table 2 reports cancer frequency (%) by sex and age at diagnosis. Among female dogs, all cancer age-specific frequency increased from 3.1% in the group aged ≤ 3 years at diagnosis to 27.1% in the group aged >11 years at diagnosis. Among males, 5.7 and 30.0% of all cancers were diagnosed in pet dogs aged ≤ 3 years and >11 years, respectively. Sixty-one percent of the cancer cases were diagnosed in crossbred and 31% in purebred dogs (data not shown).

IRs for all cancers and for selected site-specific cancers by calendar period are shown in Table 3 and Figures 3 and 4 for male and female dogs, respectively. Among male dogs, cancer incidence increased across the study period for all cancers, lymphomas, skin cancer excluding melanoma, and cancers of the connective and other soft tissue (Table 3, Fig 3). Among bitches (Table 3, Fig 4), all cancer IRs increased significantly in the calendar period 1990–1994 compared with the previous period (1985–1989), then slightly decreased in the period 1995–1999, and finally increased again in the most recent calendar period (2000–2002). The changes observed for all cancers are mainly attributable to calendar time-specific rates for mammary cancer which peaked in 1990–1994 (IR: 264.0, 95% CI: 243.5–285.9 per 100,000 dog-years) and then constantly declined to reach an IR = 181.8 (95% CI: 156.9–209.6) in 2000–2002. The incidence for site-specific cancer other than mammary increased constantly across the 4 calendar periods.

Overall, site, and sex-specific cancer frequency and IRs in dogs are shown in Table 4. The most frequently diagnosed cancers among male dogs were non-Hodgkin's lymphomas (20.1%), skin excluding melanoma (19.2%), genital organs (16.8%), and connective and other soft tissues (13.2%). Nevi and melanomas accounted for 0.7% of all cancers. Among female dogs, mammary cancer was the most frequently diagnosed (70.5%), followed by non-Hodgkin's lymphomas (8.4%), cancer of the connective and other soft tissues (4.6%), and skin cancer

Table 2. Canine tumors reported to the Animal Tumor Registry of Genoa, Italy, by malignancy, sex and age at diagnosis (years), and age-specific canine population at risk (dog-years) during the period of observation 1985–2002.

	Cancers					Noncancers		Canine Population	
	Males		Females		Total	Total		Males	Females
Age Group (years)	No.	%	No.	%	No.	No.	%	Dog-Years	
0–3	65	5.7	67	3.1	132	389	11.3	393,134	281,983
> 3–5	80	7.0	130	6.0	210	355	10.3	175,938	123,249
> 5–7	142	12.4	285	13.2	427	533	15.5	156,658	108,066
> 7–9	263	23.0	550	25.5	813	844	24.5	132,699	90,489
> 9–11	250	21.9	544	25.2	794	664	19.3	105,212	71,279
> 11	342	30.0	585	27.1	927	655	19.0	185,925	119,028
Total	1,142	100	2,161	100	3,303	3,440	100	1,149,566	794,094

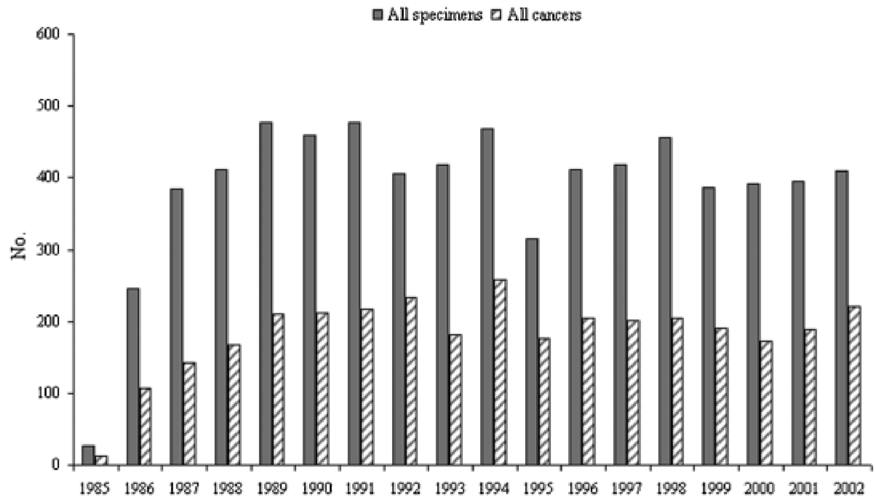

Fig 1. Submission of biological specimens across the study period (1985–2002) and number of histologically diagnosed cancers.

(3.8%). Cancer of the lip, oral cavity and pharynx, and digestive organs accounted for 2.6% of all cancers.

The IR for all cancer was 99.3 (per 100,000 dog-years) (95% CI: 93.6–105.1) and 272.1 (95% CI: 260.7–283.6) in males and female dogs, respectively (Table 4). The higher rate observed in female compared with male dogs is explained by the fact that mammary cancer was very common in females (IR: 191.8, 95% CI: 182.2–201.4) and relatively rare in male dogs (IR: 2.1, 95% CI: 1.4–3.2). The IR for non-Hodgkin's lymphoma was similar in male (IR: 19.9, 95% CI: 17.4–22.7) and in female dogs (IR: 22.9, 95% CI: 19.7–26.5). Cancer of the skin (excluding melanoma) was the only site-specific malignancy with a higher incidence in male (IR: 19.1, 95% CI:16.6–21.8) than in female dogs (IR: 10.4, 95% CI:8.3–12.9).

Age-specific IRs for all cancers and selected site-specific cancers are reported in Tables 5 and 6 for female and male dogs, respectively. All cancers incidence increased with age in both male and female dogs, the former and the latter showing 14- and 32-fold higher rates in the age group $>$9–11 years compared with the group aged $\leq$3 years (Tables 5 and 6). The markedly increased incidence for all cancers in female dogs (Table 5) was mainly, but not solely, explained by the age-related increase observed for female mammary cancer (Fig 3), the most frequently occurring site-specific cancer in bitches. Indeed, IRs also increased with age for cancer other than mammary (Fig 5), and specifically for skin cancer (excluding melanoma), cancer of the connective and other soft tissue, non-Hodgkin lymphoma, cancer of the genital organs, and lip, oral cavity, and pharyngeal cancers (Table 5). IRs for all cancers and for the above-mentioned site-specific cancers reached a plateau at age $>$9–11 years and decreased after that age (Table 5, Fig 5). The same age-specific pattern was observed for male dogs with most of the age- and site-specific IRs peaking at age $>$9–11 years and declining in dogs aged $>$11 years (Table 6, Fig 5). A clearly different age pattern was observed for non-Hodgkin lymphoma incidence both in male and female dogs with rates that peaked at an earlier age ($>$7–9 years) and then

Fig 2. Capture-recapture estimated percent distribution of the canine population of Genoa Municipality by age groups and sex (males=63.865; females=44.116; year 1994).

Table 3. Sex- and calendar period-specific incidence rates per 100,000 dog-years (IR) and their 95% confidence intervals (95% CI) for all cancers and selected cancer sites estimated for the canine population (Genoa Municipality, Italy, 1985–2002).

		Calendar Period (years)							
		1985–1989		1990–1994		1995–1999		2000–2002	
Sex/ICD-9	Site	IR	95% CI	IR	95% CI	IR	95% CI	IR	95% CI
Males									
140–208	All cancers	76.6	67.5–86.6	90.1	80.2–100.9	99.4	89.0–110.8	169.2	149.1–191.3
171	Connective and other soft tissue	10.2	7.1–14.3	13.2	9.6–17.7	13.8	10.1–18.4	17.8	11.8–26.0
173	Skin (excluding melanoma)	20.7	16.1–26.2	15.6	11.6–20.5	17.4	13.2–22.5	26.4	18.9–36.1
200,202	Non-Hodgkin's lymphoma	13.2	9.6–17.7	16.8	12.7–21.8	20.4	15.9–26.0	40.3	30.8–51.8
Females									
140–208	All cancers	167.0	150.7–184.6	349.3	326.0–374.3	281.9	260.6–304.5	312.0	279.0–347.8
171	Connective and other soft tissue	10.4	6.7–15.5	13.5	9.2–19.1	10.0	6.3–15.0	20.1	12.4–30.7
174–175	Mammary	119.2	105.5–134.2	264.0	243.5–285.9	196.6	178.9–215.6	181.8	156.9–209.6
200,202	Non-Hodgkin's lymphoma	13.9	9.5–19.6	21.7	16.1–28.7	28.3	21.8–36.0	33.5	23.3–46.6

declined (Tables 5 and 6 and Fig 6). Age-specific cancer IRs for lip, oral cavity, and pharynx increased constantly with increasing age in both female (Table 5) and male dogs (Table 6).

Discussion

Tumors frequently are diagnosed in domestic animals, and their detection and diagnosis vary according to objective difficulties and methodologic differences among veterinary cancer registries.[13] Mammary gland, genital, and skin tumors are easier to recognize by physical examination than are tumors of the respiratory tract, digestive tract, and other internal organs that require specific examinations such as X-ray, computed tomography scanning (CT), magnetic resonance imaging (MRI), and ultrasound examination. Identifying the true animal population of companion animals remains a difficult task requiring reliable scientific approaches to estimate the size of the base population and its age- and sex-specific features. This represents a serious limitation for any rigorous attempt to estimate cancer incidence in pet animals explaining the variability of the cancer IRs in canine populations reported by animal registries[4,5,7,8,10] We have tried to overcome these limitations using the ATR data set that was generated during an 18-year time period (1985–2002) and concentrating on the tumor cases that occurred among the canine populations of the Genoa Municipality that were referred to and histologically diagnosed by the ATR. The long period of observation considered allowed us to reduce the naturally occurring annual variability of cancer incidence and to compute stable rates across the entire time window 1985–2002. By restricting the observation to a defined geographic area (ie, Genoa Municipality), we were able to estimate the base population of dogs at risk and then compute site-, age-, and sex-specific cancer IRs.

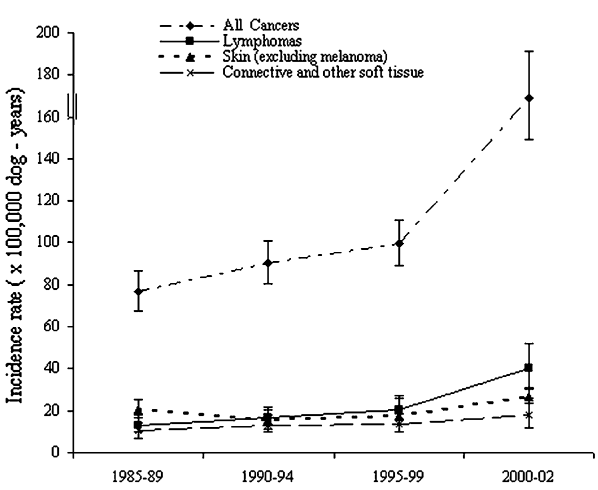

Fig 3. Male dog cancer incidence rates estimated across the study period (1985–2002) for all cancers and selected cancer sites by calendar period. Vertical bands represent the 95% confidence intervals of the estimated incidence rates.

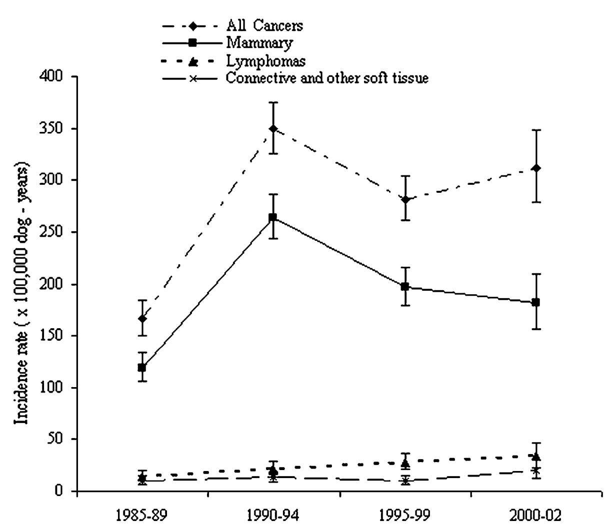

Fig 4. Female dog cancer incidence estimated across the study period (1985–2002) for all cancers and selected cancer sites by calendar period. Vertical bands represent the 95% confidence intervals of the estimated incidence rates.

Table 4. Cancer frequency (%), incidence rates per 100,000 dog-years (IR) and their 95% confidence intervals (95% CI) estimated for the canine population by sex and site (Genoa Municipality, Italy, 1985–2002).

		Gender							
		Males				Females			
ICD-9	Site	No.	%	IR	95% CI	No.	%	IR	95% CI
140–149	Lip, oral cavity, pharynx	120	10.5	10.4	8.6–12.5	56	2.6	7.0	5.3–9.2
150–159	Digestive organs, peritoneum	59	5.2	5.1	3.9–6.6	57	2.6	7.2	5.4–9.3
160–165	Respiratory, intrathoracic organs	22	1.9	1.9	1.2–2.9	22	1.0	2.8	1.7–4.2
170	Bones and articular cartilage	41	3.6	3.6	2.6–4.8	44	2.0	5.5	4.0–7.4
173	Skin (excluding melanoma)	219	19.2	19.0	16.6–21.8	83	3.8	10.4	8.3–12.9
171	Connective and other soft tissue	151	13.2	13.1	11.1–15.4	99	4.6	12.5	10.1–15.2
172	Skin melanoma	8	0.7	0.7	0.3–1.4	5	0.2	0.6	0.2–1.5
174–175	Mammary	25	2.2	2.2	1.4–3.2	1,523	70.5	191.8	182.2–201.4
179–184	Female genitourinary organs	—	—	—	—	34	1.6	4.3	3.0–6.0
185	Prostate	8	0.7	0.7	0.3–1.4	—	—	—	—
186–187	Male genitourinary organs	192	16.8	16.7	14.4–19.2	—	—	—	—
200, 202	Non-Hodgkin's lymphoma	229	20.1	19.9	17.4–22.7	182	8.4	22.9	19.7–26.5
	Other sites	68	6.0	5.9	4.5–7.4	56	2.6	4.9	3.6–6.3
140–208	All cancers	1,142	100	99.3	93.6–105.1	2,161	100	272.1	260.7–283.6

Although the frequency of biopsy specimen submission increased sharply during the first years of activity of the ATR and then remained stable through the later years, the proportion of cancers diagnosed was stable across the entire study period. This finding indicates that the ATR gained popularity within a few years of its launch, a phenomenon that is commonly observed when a novel health program is implemented and made available to the general population.

During the study period, cancer IRs increased among male dogs for all cancers and for site-specific cancers. Among bitches, all cancer incidence peaked during the calendar period 1990–1994, declined during the period 1995–1999, and increased again during the most recent period of observation 2000–2002. This calendar time-specific behavior is mainly attributable to the sharp increase of mammary cancer incidence in bitches observed during the early years of activity of the ATR that was followed by a decrease during the most recent calendar periods 1995–1999 and 2000–2002. The peak in mammary cancer incidence may result from a diagnostic anticipation that occurred in the early years of activity of the ATR. The decreased incidence for mammary cancers in female dogs that was observed in the late calendar periods may be attributable, at least in part, to the increasing frequency of spaying at a young age.[22] However, such a practice was not commonly reported in our population. Ovariohysterectomy generally was associated with uterine diseases in older bitches. Unfortunately, data on spaying are not collected by the demographic registry of the canine population of the city of Genoa. This precluded computation of spaying-specific IRs. Incidence for all of the other site-specific cancers but mammary cancer showed a monotonic increase across the entire study period.

The almost 3-fold higher incidence for all cancers that were observed in female (IR: 272.1, 95% CI: 260.7–283.6) than in male dogs (IR: 99.3, 95% CI: 93.6–105.1) was mainly explained by the high incidence of mammary cancer observed in female dogs. Skin cancer IR (excluding melanoma) was higher in males (IR:19.1, 95% CI: 16.6–21.7) than in female dogs (IR: 10.5, 95% CI: 8.3–12.9), whereas the incidence of non-Hodgkin's lymphoma was similar in male dogs (IR: 19.9, 95% CI: 17.4–22.7) and bitches (IR: 22.9, 95% CI: 19.7–26.5). Cancer incidence clearly was associated with age. For all cancers and most site-specific cancers, IRs increased with age, peaked in the age group >9–11 years and then declined in dogs aged >11 years. Lymphoma incidence also was associated with age, reaching its highest rate at age >7–9 years and decreasing in older dogs. This finding is in agreement with the age-specific incidence reported by Dorn et al[4,23] and in contrast with the peak incidence detected by Edwards et al[24,25] in dogs aged 10 years. The different age-related incidence peaks for lymphoma may reflect a different age structure of the population of UK insured dogs compared with the canine populations of the Italian ATR and the California ANR, the former pet population at risk being younger than the latter two.

We have estimated crude, age, and sex-specific IRs for all cancers and for site-specific cancers in a geographically defined population of dogs over a time period of 18 years. We believe these rates are reliable estimates of the occurrence of cancer in dogs in the Municipality of Genoa. However, because a biopsy specimen was required to make a histopathologic diagnosis of cancer and given that biopsies for tumors of internal organs (eg, respiratory and digestive tract neoplasms) were rarely available to the ATR, IRs for internal organs are likely to have been underestimated. Moreover, our estimated average canine population was based on a capture-recapture methodology that relies on underlying assumptions which may have been violated leading to a biased estimate of the canine population. The violation of the assumption of independence of the 2 sources that were used can be excluded because the ATR and

Table 5. Site- and age-specific incidence rates (IR) per 100,000 dog-years and their 95% confidence intervals (95% CI) estimated for the female canine population (Genoa Municipality, Italy, 1985–2002).

		Age Group (years)											
		0–3		> 3–5		> 5–7		> 7–9		> 9–11		> 11	
ICD-9	Site	IR	95% CI	IR	95% CI	IR	95% CI	IR	95% CI	IR	95% CI	IR	95% CI
140–149	Lip, oral cavity, pharynx	1.4	0.4–3.6	—	—	3.7	1.0–9.5	9.9	4.5–18.9	16.8	8.7–29.4	22.6	14.9–33.0
150–159	Digestive organs, peritoneum	0.3	0.0–2.0	2.4	0.5–7.1	6.5	2.6–13.3	18.8	10.9–30.0	21.0	11.7–34.7	11.8	6.4–19.7
160–165	Respiratory, intrathoracic organs	—	—	0.8	0.0–4.5	3.7	1.–9.5	2.2	0.3–8.0	8.4	3.1–18.3	7.6	3.5–14.3
170	Bones and articular cartilage	0.7	0.1–2.7	2.4	0.5–7.1	2.7	0.6–8.1	9.9	4.5–18.9	18.2	9.7–31.1	11.7	6.4–19.7
173	Skin (excluding melanoma)	0.7	0.1–2.6	6.4	2.8–12.8	12.9	7.1–21.7	11.0	5.3–20.3	26.7	16.0–41.6	25.2	17.0–35.9
171	Connective and other soft tissue	2.1	0.8–4.6	4.1	1.3–9.5	10.2	5.1–18.2	15.5	8.5–25.9	37.9	24.9–55.1	30.2	21.1–41.8
172	Skin melanoma	—	—	—	—	1.8	0.2–6.7	2.2	0.3–8.0	—	—	0.8	0.0–4.7
174–175	Mammary	10.6	7.1–15.1	62.5	49.3–78.1	181.4	156.9–208.6	461.9	418.7–508.4	561.2	507.5–619.0	337.7	305.5–372.4
179–184	Female genitourinary organs	1.8	0.6–4.1	—	—	0.9	0.0–5.1	8.8	3.8–17.4	14.0	6.7–25.8	8.4	4.0–15.4
200, 202	Non-Hodgkin's lymphoma	5.7	3.2–9.2	21.9	14.4–31.9	35.2	24.8–48.2	47.5	34.4–64.0	42.1	28.4–60.1	23.5	15.6–34.0
	Other sites	0.3	0.0–2.0	4.9	1.8–10.6	4.6	1.5–10.8	19.9	11.7–31.4	16.8	8.7–29.4	11.8	6.4–19.7
140–208	All cancers	23.7	18.4–30.1	105.5	88.1–125.2	263.7	234.0–296.1	607.8	558.1–660.8	763.2	700.4–830.1	491.5	452.5–533.0

Table 6. Site- and age-specific incidence rates per 100,000 dog-years (IR) and their 95% confidence intervals (95% CI) estimated for the male canine population (Genoa Municipality, Italy, 1985–2002).

		Age Group (years)											
		0–3		> 3–5		> 5–7		> 7–9		> 9–11		> 11	
ICD-9	Site	IR	95% CI	IR	95% CI	IR.	95% CI	IR	95% CI	IR	95% CI	IR	95% CI
140–149	Lip, oral cavity, pharynx	0.5	0.1–1.8	1.7	0.3–5.0	5.1	2.2–10.1	17.3	11.0–26.0	25.7	16.9–37.3	30.7	23.2–39.7
150–159	Digestive organs, peritoneum	0.5	0.1–1.8	3.4	1.2–7.4	3.2	1.0–7.5	8.3	4.1–14.8	19.0	11.6–29.3	8.1	4.5–13.3
160–165	Respiratory, intrathoracic organs	—	—	0.6	0.0–3.1	1.3	0.1–4.6	4.5	1.7–9.8	7.6	3.3–15.0	2.7	0.9–6.2
170	Bones and articular cartilage	1.3	0.4–3.0	—	—	7.0	3.5–12.6	8.3	4.1–14.8	9.5	4.6–17.5	2.1	0.6–5.5
173	Skin (excluding melanoma)	0.5	0.1–1.8	5.7	2.7–10.4	14.7	9.3–22.0	35.4	26.0–47.1	56.1	42.7–72.3	41.9	33.1–52.3
171	Connective and other soft tissue	2.8	1.4–5.0	6.2	3.1–11.1	9.6	5.4–15.8	24.9	17.1–34.9	27.6	18.4–39.6	28.0	20.9–36.7
172	Skin melanoma	0.2	0.0–1.4	—	—	0.6	0.0–3.6	0.7	0.0–4.2	1.9	0.2–6.9	1.6	0.33–4.7
174–175	Mammary	—	—	0.6	0.0–3.2	2.5	0.7–6.5	6.8	3.1–12.9	2.85	0.6–8.3	4.3	1.9–8.5
186–187	Male genitourinary organs	2.0	0.9–4.0	3.4	1.2–7.4	14.0	8.8–21.2	29.4	20.9–40.2	42.8	31.2–57.2	38.7	30.3–48.7
200,202	Non-Hodgkin's lymphoma	6.7	4.1–9.4	19.9	13.9–27.7	26.8	19.3–36.2	44.5	33.8–57.3	35.2	24.8–48.5	16.7	11.3–23.6
	Other sites	2.3	1.0–4.3	4.0	1.6–8.2	5.7	2.6–10.9	18.1	11.6–26.9	9.5	4.6–17.5	9.1	5.3–14.6
140–208	All cancers	16.5	12.8–21.1	45.5	36.1–56.6	90.6	76.3–106.8	198.2	174.9–223.6	237.6	209.1–269.0	183.9	164.9–204.5

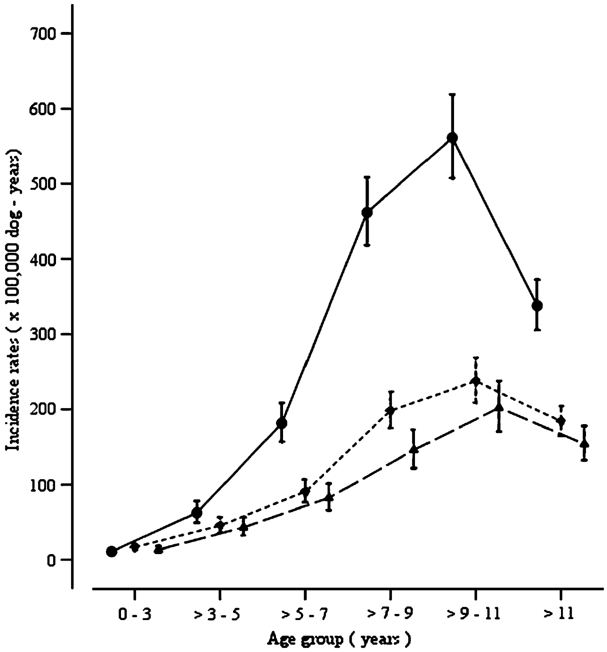

Fig 5. Age-specific incidence rates for mammary cancer (full line) and cancers other than mammary (dotted lines) in female dogs and for all cancers in male dogs (dashed line) (1985–2002). Vertical bands represent the 95% confidence intervals of the estimated incidence rates.

the CDR were established with different purposes and the cancer registry is not nested within the demographic registry. Violation of the assumption that the canine population under study is closed (ie, no entries or losses)

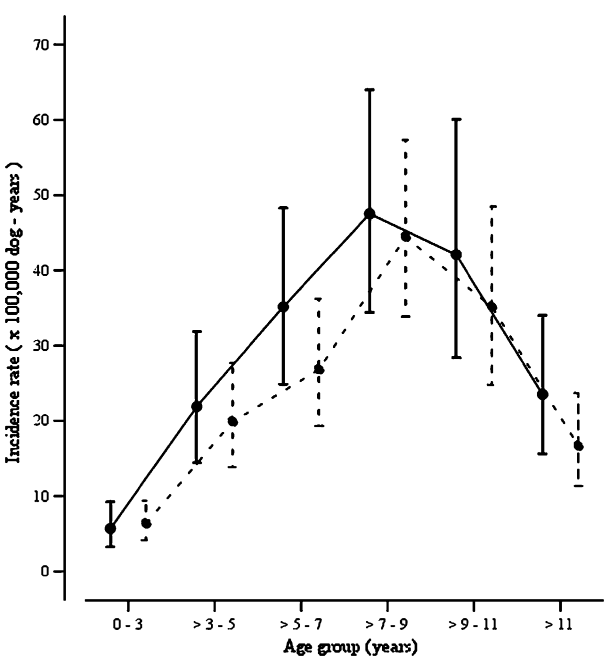

Fig 6. Age- and sex-specific incidence rates for non-Hodgkin's lymphoma (1985–2002). Females=full line, males=dotted line. Dots represent incidence rate point estimates and vertical bands their 95% confidence intervals.

is of specific concern given the duration of the study period (18 years), normal canine longevity, and the expected deaths across the study interval. However, violation of the closure assumption because of births or deaths only (applicable to our study) does not result in a biased estimation of the population size, although it decreases precision.[18] For this reason, we provided the 95% CI around each point estimate of the IR that must be taken into account when considering the likely true incidence.

Further analyses of our data sets will include investigation of environmental and individual risk factors, including breed susceptibility to cancer in pet dogs. It has been claimed that cancer occurrence in dogs may warn of possible environmental causes of cancers in humans for specific geographic areas. However, the limited number of published studies on the association of environmental exposures and cancer occurrence in dogs have been conducted only after potential health risks in humans have been reported[26–31] as supportive evidence for the causality of the associations detected in studies of human patients. An exception is the preliminary finding from an Italian study suggesting a possible role of sheep as sentinel animals to evaluate environmental diffusion of naturally occurring fibrous amphiboles potentially involved in the occurrence of pleural mesotheliomas in humans.[32] Conversely, research based on spontaneous cancers in pet or free-living animals has expanded in the fields of mechanisms of carcinogenesis and cancer treatment for clinical application in companion animals.[33,34] Some 41,000 formalin-fixed, paraffin-embedded biopsies archived by the ATR represent a unique repository for future research based on genomic technologies aimed at identifying common or different biological mechanisms leading to spontaneous cancers in animals and humans. Given the unique opportunity as models for human cancer biology and for translational cancer therapeutics, the companion animal registries remain critical in providing unbiased animal populations to investigate cancer occurrence in animals, to study the role of environmental and genetic factors in cancer etiology, and to plan clinical trials for the assessment of new drug efficacy and toxicity.

Footnotes

[a] Stata Statistical Software release 7.0, 1999, Stata Corporation, College Station, TX

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References

1. von Leyden EKMWE, von Hansemann D, Meyer G. eds. Berichte uber die vom Komitee fur Krebsforschung am 15 Oktober 1900 erhobene Sammelforschung. Jena: Gustav Fischer; 1902.

2. Keding G. Annotation zur Krebsepidemiologie. Arzteblatt 1973;27; cited in G Wagner, History of cancer registration. In: OM Jensen, DM Parkin, R MacLennan, et al. (eds). Cancer Registration: Principles and Methods, IARC Scientific Publication No. 95, Lyon, France: International Agency for Research on Cancer; 1991; 1–4.

3. Parkin DMWSFJ, Teppo L, Thomas DB. Cancer Incidence in Five Continents, Vol. VIII. IARC Publ No 155. Lyon, France: International Agency for Research on Cancer; 2003.

4. Dorn CR, Taylor DO, Schneider R, et al. Survey of animal neoplasms in Alameda and Contra Costa Counties, California. II. Cancer morbidity in dogs and cats from Alameda County. J Natl Cancer Inst 1968;40:307–318.

5. Priester WA, McKay FW. The occurrence of tumors in domestic animals. Natl Cancer Inst Monogr 1980;1–210.

6. MacVean DW, Monlux AW, Anderson PS Jr, et al. Frequency of canine and feline tumors in a defined population. Vet Pathol 1978;15:700–715.

7. Merlo DF, Capurro C, Reggiardo G, et al. Cancer incidence rates in dogs: Preliminary findings from the Animal Tumor Registry, Genova, Italy. In: Rossi L, Richardson R, Harshbarger J, eds. Spontaneous Animal Tumors: A Survey. Proceedings of the First World Conference on Spontaneous Animal Tumors 1995 Apr 28–30. Genoa (Italy); 2000:135–139.

8. Reid-Smith RJ, Bonnett BN, Martin SW, et al. The incidence of neoplasia in the canine and feline patient populations of private veterinary practices in southern Ontario. Proceedings of the 9th Symposium of the International Society for Veterinary Epidemiology and Economics, Breckenridge, CO, August 6–11, 2000, 935–955.

9. Bonnett BN, Egenvall A, Olson P, Hedhammar A. Mortality in insured Swedish dogs: Rates and causes of death in various breeds. Vet Rec 1997;141:40–44.

10. Dobson JM, Samuel S, Milstein H, et al. Canine neoplasia in the UK: Estimates of incidence rates from a population of insured dogs. J Small Anim Pract 2002;43:240–246.

11. Launching a dog cancer registry in Piedmont. Epidemiol Prev 2003;27:12.

12. World Health Organization. International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). Geneva, Switzerland: World Health Organization; 1999.

13. Brønden LBFA, Kristensen AT. Veterinary cancer registries in companion animal cancer: A review. Vet Comp Oncol 2007;5:133–144.

14. Goldschmidt MH, Shofer FS. Skin Tumors of the Dog and Cat. Oxford, UK: Pergamon Press; 1992.

15. World Health Organization. International Classification of Diseases. Ninth Revision. Geneva, Switzerland: World Health Organization; 1978.

16. World Health Organization. International Classification of Diseases for Oncology, 2nd ed. Geneva, Switzerland: World Health Organization; 2001.

17. International Working Group for Disease Monitoring and Forecasting. Capture-recapture and multiple-record systems estimation I: History and theoretical development. Am J Epidemiol 1995;142:1047–1058.

18. Kendall WL. Robustness of closed capture-recapture methods to violations of the closure assumptions. Ecology 1999;80: 2517–2525.

19. Pollock KH. Modeling capture, recapture, and removal statistics for estimation of demographic parameters for fish and wildlife populations: Past, present, and future. J Am Stat Ass 1991; 86:225–238.

20. Hook EB, Regal RR. Capture-recapture methods in epidemiology: Methods and limitations. Epidemiol Rev 1995;17: 243–264.

21. Wittes JT, Colton T, Sidel VW. Capture-recapture methods for assessing the completeness of case ascertainment when using multiple information sources. J Chronic Dis 1974;27:25–36.

22. Schneider R, Dorn CR, Taylor DO. Factors influencing canine mammary cancer development and postsurgical survival. J Natl Cancer Inst 1969;43:1249–1261.

23. Dorn C, Taylor DO, Schneider R, et al. Survey of animal neoplasms in Alameda and Contra Costa Counties, California. II. Cancer morbidity in dogs and cats from Alameda County. J Natl Cancer Inst 1968;40:307–318.

24. Edwards DS, Henly WE, Harding EF, et al. Breed incidence of lymphoma in a UK population of insured dogs. Vet Comp Oncol 2003;1:200–206.

25. Edwards DS, Henly WE, Harding EF, et al. Breed incidence of lymphoma in a UK population of insured dogs. Veterinary and Comparative Oncology 2003;1:200–206.

26. Backer LC, Grindem CB, Corbett WT, et al. Pet dogs as sentinels for environmental contamination. Sci Total Environ 2001;274:161–169.

27. Glickman LT, Domanski LM, Maguire TG, et al. Mesothelioma in pet dogs associated with exposure of their owners to asbestos. Environ Res 1983;32:305–313.

28. Hayes HM, Tarone RE, Cantor KP, et al. Case-control study of canine malignant lymphoma: Positive association with dog owner's use of 2,4-dichlorophenoxyacetic acid herbicides. J Natl Cancer Inst 1991;83:1226–1231.

29. Hayes HM, Tarone RE, Casey HW, Huxsoll DL. Excess of seminomas observed in Vietnam service U.S. military working dogs. J Natl Cancer Inst 1990;82:1042–1046.

30. Pettersson A., Richiardi L, Nordenskjold A, et al. Age at surgery for undescended testis and risk of testicular cancer. N Engl J Med 2007;356:1835–1841.

31. Reif JS, Lower KS, Ogilvie GK. Residential exposure to magnetic fields and risk of canine lymphoma. Am J Epidemiol 1995;141:352–359.

32. DeNardo P., Bruni B, Paoletti L, et al. Pulmonary fibre burden in sheep living in the Biancavilla area (Sicily): Preliminary results. Sci Total Environ 2004;325:51–58.

33. Argyle DJ, Madewell BR. Comparative oncology new and expanding opportunities for research. VetComp Oncol 2003;1: 65–66.

34. Vail DM, MacEwen EG. Spontaneously occurring tumors of companion animals as models for human cancer. Cancer Invest 2000;18:781–792.