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Review

Shark Cartilage, Cancer and the Growing Threat of Pseudoscience

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Abstract

The promotion of crude shark cartilage extracts as a cure for cancer has contributed to at least two significant negative outcomes: a dramatic decline in shark populations and a diversion of patients from effective cancer treatments. An alleged lack of cancer in sharks constitutes a key justification for its use. Herein, both malignant and benign neoplasms of sharks and their relatives are described, including previously unreported cases from the Registry of Tumors in Lower Animals, and two sharks with two cancers each. Additional justifications for using shark cartilage are illogical extensions of the finding of antiangiogenic and anti-invasive substances in cartilage. Scientific evidence to date supports neither the efficacy of crude cartilage extracts nor the ability of effective components to reach and eradicate cancer cells. The fact that people think shark cartilage consumption can cure cancer illustrates the serious potential impacts of pseudoscience. Although components of shark cartilage may work as a cancer retardant, crude extracts are ineffective. Efficiencies of technology (*e.g.,* fish harvesting), the power of mass media to reach the lay public, and the susceptibility of the public to pseudoscience amplifies the negative impacts of shark cartilage use. To facilitate the use of reason as the basis of public and private decision-making, the evidence-based mechanisms of evaluation used daily by the scientific community should be added to the training of media and governmental professionals. Increased use of logical, collaborative discussion will be necessary to ensure a sustainable future for man and the biosphere.

Introduction

Until this century, it was difficult to imagine that anthropogenic activities would endanger the existence of an entire class of animals in the open sea. A combination of efficient fishing technologies, susceptibility of the public to erroneous arguments, and the power of television to rapidly shape opinion has now contributed to depletions of shark populations measurable in 8 to 15 years (1). Layers of fallacious arguments, dissected below, have successfully convinced desperate cancer patients to buy ineffective products that distract them from proven or potentially useful therapies. These events comprise a wake-up call to find ways for our civilization to check negative impacts caused by combinations of poor reasoning and/or poor intentions with powerful technologies.

The direct causes of the drop in shark populations are potentially attributable to a combination of indiscriminate fishing and purposeful harvesting of sharks, primarily for their fins as food and for their cartilage as folk medicine. Crude cartilage extracts are sold as a nontraditional remedy for a variety of human ailments, including cancer. Here, we highlight the falsehoods and erroneous reasoning as justifications for using crude shark cartilage extracts to cure cancer. A primary justification for using crude shark cartilage extracts to treat cancer is based on the misconception that sharks do not, or infrequently, develop cancer. Other justifications represent overextensions of experimental observations: concentrated extracts of cartilage can inhibit tumor vessel formation and tumor invasions (*e.g.,* refs. 2–5). No available data or arguments support the medicinal use of crude shark extracts to treat cancer (6).

The claims that sharks do not, or rarely, get cancer was originally argued by I. William Lane in a book entitled "Sharks Don't Get Cancer" in 1992 (7), publicized in "60 Minutes" television segments in 1993, and reargued in another book in 1996 (8). The titles of the books do not match their texts in which the authors note that sharks actually get cancer but claim incorrectly that sharks rarely get cancer. We make three main points below: (*a*) sharks do get cancer; (*b*) the rate of shark cancer is not known from present data; and (*c*) even if the incidence of shark cancer were low, cancer incidence is irrelevant to the use of crude extracts for cancer treatment.

Materials and Methods

We examined tumors occurring among members of the Class Chondrichthyes, which includes the closely related sharks, skates, rays, and chimaeroids. Members of this class are considered by most specialists to have originated monophyletically in a straight line of evolutionary descent (9), and all chondrichthyans share at least 17 primary characteristics, including a cartilaginous endoskeleton devoid of bone-producing osteoblasts. Thus, although they have diverged in body form, they continue to share ancestral traits that establish scientific identity as chondrichthyans regardless of what they are commonly called.

Chondrichthyan neoplasms described in the literature were reviewed, and cases deposited in the Registry of Tumors in Lower Animals were examined. All cases were tabulated (Table 1) along with selected descriptive information. Obsolete or inaccurate scientific names were replaced with current names when this could be determined from the peer-reviewed literature or from consultations with taxonomists at the National Museum of Natural History, Smithsonian Institution (Washington, D.C.).

Three previously unknown cases of sharks presenting with tumors included two spiny dogfish sharks, *Squalas acanthias*, and one tiger shark, *Galeocerdo cuvier*. The spiny dogfish cases were received as formalin-fixed tissue specimens that incorporated the tumor masses. The masses were described and photographed as gross specimens. The tissues were then processed, embedded, microtomed, and stained according to routine histologic methods for the preparation of microscope slides. The tiger shark case was received as microscope slides, photographs, and a tentative evaluation (Thierry M. Work). The final diagnoses for all three cases were based on the consensus opinion of four pathologists who have expertise in medical, veterinary, or fish tumor pathology.

Results

A History of Known Shark Tumors. Because cartilage is most commonly extracted from organisms with cartilaginous backbones, we looked for tumors in the class Chondrichthyes, which includes the closely related sharks, skates, rays, and chimaeroids and share a common phylogeny (9).

Forty-two cases of malignant or benign chondrichthyan tumors were found in the literature and the Registry of Tumors in Lower Animals

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Table 1 *Neoplasias from class chondrichthyes in the collection of the Registry of Tumors in Lower Animals (RTLA) and/or in the literature*

Species	RTLA no.	Location	Diagnosis	Ref. no.
Order Chimaeriformes (chimaeras)				
Family Chimaeridae (ratfish)				
Spotted ratfish, *Hydrolagus colliei*	416	Puget Sound, WA	Myxosarcoma	19
Spotted ratfish, *Hydrolagus colliei*	3409	Vancouver Island, British Columbia, Canada	Olfactory neuroblastoma	
Order Lamniformes (mackerel sharks)				
Family Odontospididae (sand tiger sharks)				
Sand tiger shark, *Carcharias taurus*	3797	New England Aquarium, Boston, MA	Chromaffinoma	
Sand tiger shark, *Carcharias taurus*	6434	Sea World of Florida, Orlando, FL	Mucoepidermoid papilloma of the maxillary gingiva	61
Order Orectolobiformes (carpet sharks)				
Family Ginglymostomatidae (nurse sharks)				
Tawny nurse shark, *Nebrius ferrugineus*		Oceanaáio de Lisboa, Lisbon, Portugal	Osteoma	62
Order Carcharhiniformes (ground sharks)				
Family Carcharhinidae (requiem sharks)				
Blacktip shark, *Carcharhinus limbatus*	5950	Mirage Hotel aquarium, Las Vegas, NV	Cutaneous fibrosarcoma	
Blue shark, *Prionace glauca**		Black Sea	Hepatocellular carcinoma†	11, 12
Blue shark, *Prionace glauca*	7300	Off Montauk Point, Long Island, NY	Cholangiocarcinoma; mesothelioma	21
Bull shark, *Carcharhinus leucas*	212	Mote Marine Laboratory, Sarasota, FL	Cutaneous fibroma	18
Sandbar shark, *Carcharhinus plumbeus*‡	523	Gulf of Mexico, Sarasota, FL	Lymphoma, metastatic adenocarcinomas (unknown primary)	16, 17
Tiger shark, *Galeocerdo cuvier*	6887	Pacific Ocean, HI	Cutaneous fibroma	
Family Scyliorhinidae (cat sharks)				
Nursehound, *Scyliorhinus stellaris*§			Enteric adenoma/carcinoma	63
Nursehound, *Scyliorhinus stellaris*§			Cutaneous odontoma	64
Cat shark, *Scyliorhinus catulus*			Cutaneous epithelioma	15
Small-spotted cat shark, *Scyliorhinus canicula*			Cutaneous osteoma	65
Small-spotted cat shark, *Scyliorhinus canicula*			Cutaneous chondroma	65
Swell shark, *Cephaloscyllium ventriosum*	5207		Hypodermal lipoma	
Swell shark, *Cephaloscyllium ventriosum*		Florida Aquarium	Hepatic capsular fibroma	66
Family Triakidae (houndsharks)				
Dusky smooth-hound, *Mustelus canis*	4464	Atlantic Ocean off Cape Hatteras, NC	Epidermal papilloma	67
Order Squaliformes (dogfish sharks)				
Family Squalidae (dogfish sharks)				
Longnose spurdog *Squalus blainvillei*¶	938	Duck Cove, New Zealand	Neurofibroma	68
Spiny dogfish, *Squalus acanthias*	1221	Frenchman's Cove, ME	Choroid plexus papilloma	20
Spiny dogfish, *Squalus acanthias*	3144	North Atlantic Ocean	Chondroma, vertebral	
Spiny dogfish, *Squalus acanthias*	3172	North Atlantic Ocean	Renal carcinoma	
Spiny dogfish, *Squalus acanthias*			Fibroepithelial lip polyp	15
Spiny dogfish, *Squalus acanthias*‖		Pacific coast, Canada	Thyroid carcinoma	13
Shortspine spurdog, *Squalus mitsukurii*			Chondroma of lumbar vertebrae	69
Order Rajiformes (skates)				
Family Rajidae (skates)				
Gray skate, *Dipturus batis***		Rathlin-a-Milley, Ireland	Cutaneous melanoma, invasive	23
Gray skate, *Dipturus batis***		County Kerry, Ireland	Cutaneous melanoma	24
Gray skate, *Dipturus batis***		Dubh Artach Light, Scotland	Cutaneous melanoma, metastatic	24
Gray skate, *Dipturus batis*††		Plymouth, United Kingdom	Cutaneous fibrosarcoma	15
Thornback skate, *Raja clavata*	4738	Thames River estuary, United Kingdom	Epidermal papilloma	70
Thornback skate, *Raja clavata*			Cutaneous melanoma, invasive	25
Thornback skate, *Raja clavata*		Port Erin Bay, Ireland	Cutaneous melanoma, invasive	26
Thornback skate, *Raja clavata*		Fleetwood, United Kingdom	Cutaneous melanoma, metastatic	24
Thornback skate, *Raja clavata*			Cutaneous fibroma	24
Thornback skate, *Raja clavata*			Fibroma	10
Thornback skate, *Raja clavata*			Cutaneous myxofibroma	24
Thorny skate, *Amblyraja radiata*	636	North Atlantic Ocean	Seminoma	71
Twineye skate, *Raja miratelus*			Cutaneous hemangioma	22
Order Myliobatiformes (stingrays)				
Family Dasyatidae (whiptail stingrays)				
Red stingray, *Dasyatis akajei*	1851	Uneo Zoo Aquarium, Tokyo, Japan	Hepatocellular adenoma‡‡	71, 72
Stingray (species unknown)	6251	St. Lucie River System, FL	Melanocytic nevus	
Stingray, *Dasyatis* sp.			Subcutaneous fibrous hemangioma	73

* The common and scientific names have been updated (originally cited as sand shark, *Prionace glaucus*).

† Although the original publication documents an adenoma, subsequent reanalysis suggests that the lesion was actually a hepatocellular carcinoma as evidenced by the invasive margins. (J. Harshbarger and G.K. Ostrander, unpublished data.)

‡ The original report of this neoplasm (16) was of a reticulum cell sarcoma in a brown shark (*Carcharinus milberti*). The species name, common name and diagnosis were subsequently revised (17) as indicated.

§ Originally reported as *Scyllium catulus*.

¶ The original report incorrectly listed this individual as a spiny dogfish, *Squalus acanthias*.

‖ Originally reported as *Squalus sucklii*.

** Formerly known as the blue skate.

†† Orginally reported as a blue skate, *Raia macrorhynchus*.

‡‡ Originally reported as hepatocytic adenoma.

(Table 1). The tumors were widely distributed across at least 21 species in nine families among seven orders, including 24 sharks, 16 skates or rays, and 2 chimaeroids. Most of the animals were collected fortuitously from both offshore and inshore locations in the Atlantic and Pacific Oceans, and a few animals came from public aquaria. Tumors originating from the nervous, digestive, integumentary, excretory, hematopoietic, reproductive, skeletal, and endocrine systems were found, and at least 15 tumors were considered malignant based on invasion into normal tissue.

Chondrichthyan neoplasms have been known for >150 years. The first, described by Deslongchamps in 1853 (10), was a 30-cm pedunculated fibroma at the base of the tail of a thornback skate, *Raja clavata*. In 1908, a liver cell tumor diagnosed as an adenoma was

reported in a blue shark, *Prionace glauca* (ref. 11, discussed in ref. 12). The lesion consisted of multiple, walnut-sized, white nodules, histologically resembling smaller-than-normal hepatocytes. Invasion by the neoplastic cells into normal hepatic parenchyma at the tumor's edge dictates a diagnosis of the malignant tumor, hepatocellular carcinoma, rather than adenoma.

A thyroid neoplasm was reported in one of 217 spiny dogfish sharks collected in the Straights of Georgia in 1913 and 1914 (13). The lesion had invaded through its capsule, and it was histologically described as ". . . solid cell masses taking the place of thyroid follicles and infiltrating interstitial tissue," consistent with poorly differentiated adenocarcinoma. By 1948, 16 neoplasms in chondrichthyans had been reported, of which at least 6, including 1 metastatic melanoma, were considered cancerous (12). Subsequently reported cases include a squamous cell carcinoma (then called epithelioma) in a cat shark, *Scyliorhinus catulus* (ref. 14, also reviewed by Wellings in ref. 15), a reticulum cell sarcoma in a brown shark, *Carcharhinus milbertii* [ref. 16, subsequently revised to a lymphoma in a sandbar shark, *Carcharhinus plumbeus* (17)], a fibroma in a bull shark, *Carcharinus leucas* (18), a myxosarcoma in a chimaeroid (*i.e.,* spotted ratfish, *Hydrolagus colliei*; ref. 19), and a choroid plexus papilloma in a spiny dogfish shark (20). It is, of course, impossible to confirm all of the old diagnoses without tissue sections. However, these shark and related chondrichthyan tumors, together with the new Registry of Tumors in Lower Animals cases described below, total 42. Two of these cases include animals that presented with two types of lesions (Table 1 and refs. 11, 12, 21). Other chondrichthyan cancers reported include a cutaneous fibrosarcoma in a gray skate, *Dipturus batis* (22), and melanomas in three gray skates (23, 24) and three thornback skates, *Raja clavata* (25, 26). In two of these six cases, the melanomas were metastatic, and in at least three others, the melanomas were locally invasive.

To additionally illustrate the existence of neoplasia in sharks, two of three previously unpublished shark tumors from the Registry of Tumors in Lower Animals are described below: a renal cell carcinoma and a chondroma. The renal cell carcinoma (RTLA case 3172) was received in 1984 as a 15-cm segment of dorsal body wall from a spiny dogfish shark containing a kidney with a tumor. Four masses, from 1.0- to 2.5-cm in diameter, protruded ventrally from the kidney (Fig. 1*A*). Two of the masses were centrally necrotic. The histologic features of this tumor, including invasion, high mitotic activity, poor differentiation, and necrosis (Fig. 1, *B* and *C*), are clearly consistent with malignancy and diagnostic of a well-differentiated adenocarcinoma of renal origin. The second tumor (RTLA case 3144) was collected in 1983 and submitted as a 13-cm section of vertebral column spiny dogfish shark with associated dorsal and lateral musculature (Fig. 1*D*). The neoplasm was a well-demarcated, 7 × 3.6-cm, geode-like hollow, oval mass attached to dorsal retroperitoneal tissue

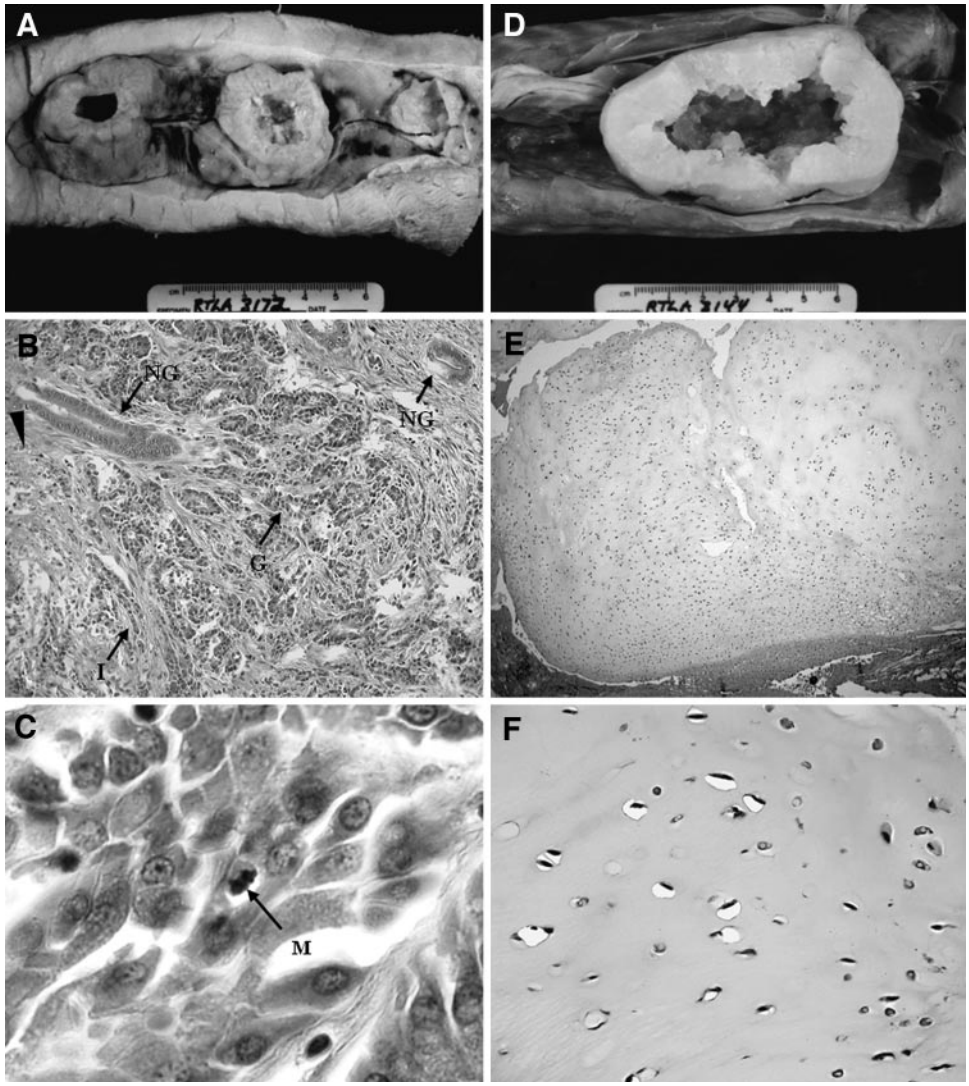

Fig. 1. A malignant kidney tumor (*A–C*) and a benign cartilage tumor (*D–F*) from spiny dogfish sharks (*Squalus acanthias*) found off the coast of Maine and donated to the Registry of Tumors in Lower Animals via the Maine Department of Natural Resources. *A–C*, a renal cell carcinoma from a RTLA case 3172 collected in 1984. *A*, ventral view of the submitted specimen, consisting of a 15-cm section of formalin-fixed skinless dorsal body wall with attached kidney. The masses protruded ventrally from the kidney and consisted of four contiguous, 1.0- to 2.5-cm masses of the same color and texture as normal kidney with confluent areas of necrosis. Sectioning revealed the hollow interior of the left and central masses (*A*). *B*, medium power view showing invasion of normal renal parenchyma. NG, normal glandular structures, most likely renal tubules. G, irregular glands formed by the tumor cells. I, rows of single malignant tumor cells invading stroma. *Arrowhead*, necrosis. The malignant cells contain similar pink refringent cytoplasmic bodies as in normal kidney tubules, consistent with renal origin (×200). *C*, high power view of renal carcinoma. M, mitosis (×1000). *D–F*, chondroma (RTLA case 3144). *D*, ventral view of the submitted 13-cm segment of dorsal body wall containing a 7.0 × 3.6 cm, oval, hollow mass projecting ventrally into the peritoneal cavity. The neoplasm was attached to the normal vertebral cartilage (data not shown). *E*, low power view showing the nodularity of the tumor. Compared with the normal cartilage, the mass has increased cellularity and a loosely fibrinous texture, and lacks the calcified perimeter apparent on normal vertebral cartilage (×50). *F*, high power view of the chondroma showing irregularly placed cartilage cells in an immature cartilagenous matrix (×500).

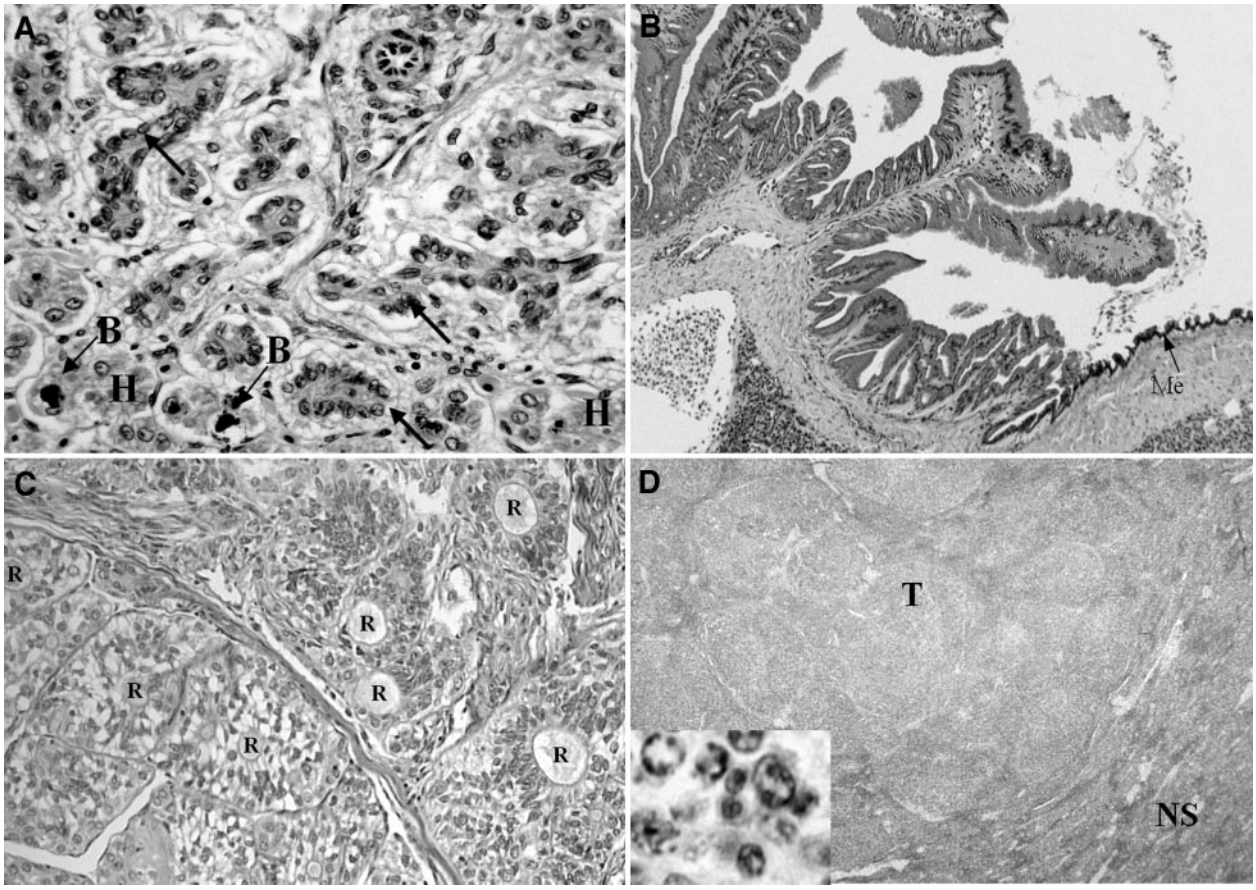

Fig. 2. Four other representative chondrichthyan malignancies. *A*, cholangiocarcinoma from a blue shark, *Prionace glauca* (RTLA case 7300). *Arrows*, malignant bile ducts; H, hepatocytes; B, bile accumulations in hepatocytes (×750). *B*, mesothelioma on the surface of the liver of the same blue shark as *A*. The tumor comprising the left two thirds of the image has a well-differentiated columnar epithelium in a convoluted, papillary architecture. Me, normal mesothelium (×25). *C*, olfactory neuroblastoma from the head of a spotted ratfish, *Hydrolagus collei* (RTLA case 3409). R, Rosette (×400). *D*, nodular (predominantly large cell) follicular lymphoma, grade 3, from a sandbar shark, *Carcharhinus plumbeus* (RTLA case 523), originally diagnosed as a reticulum cell sarcoma. T, tumor; NS, normal spleen (×25). *Inset*, ×800.

(vertebral column). The ventral part of the tumor had been removed, revealing 1- to 1.5-cm thick walls; why the center was missing is not clear. A central transverse section of the specimen showed that the mass was associated with the ventral surface of the vertebral cartilage (data not shown). The tumor appeared to arise from beneath the centrum and to pass through an interruption in the calcified perimeter of the vertebra. Microscopically, the tumor consisted of nodular masses of immature cartilage containing chondrocytes of varying density (Fig. 1, *E* and *F*). The histologic appearances of the tumor cells, together with the tumor's well-demarcated rather than invasive border, are consistent with a diagnosis of chondroma, a benign tumor of cartilage. Thus, sharks get cancer, and even their cartilage is susceptible to neoplasia.

A sampling of four chondrichthyan malignancies is shown in Fig. 2. These tumors include a cholangiocarcinoma of the liver of a blue shark (RTLA case 7300; Fig. 2*A*), a mesothelioma in the same blue shark (Fig. 2*B*), an olfactory neuroblastoma of a spotted ratfish (RTLA case 3409; Fig. 2*C*), and a nodular (predominantly large cell) follicular lymphoma, grade 3, of a sandbar shark (RTLA case 523; Fig. 2*D*), originally diagnosed with the outdated term, reticulum cell sarcoma. The invasive, nonpatent, immature bile ducts (Fig. 2*A*, arrows) in the cholangiocarcinoma had a myxoid matrix and invaded the hepatic parenchyma (livers cells; Fig. 2*A*, "H"). This particular tumor was present in a background of cirrhosis, indicated by focal fibrosis (data not shown), and bile deposition in many of the liver cells (Fig. 2*A*, "B"). The mesothelioma present on the surface of the liver of the same shark showed florid overgrowth of the mesothelium on large papillae (the left two thirds of Fig. 2*B*), which stands in stark contrast to the simple, flat, normal mesothelium (Fig. 2*B*, "Me") occupying the right third of the surface shown in Fig. 2. The olfactory neuroblastoma was an invasive, suprapalatal tumor consistent with olfactory origin, which showed formation of abundant rosettes (Fig. 2*C*, "R"). The lymphoma consisted of large, poorly differentiated cells arranged in large nodules visible at low power (adjacent tumor nodules occupy most of the center of Fig. 2*D* ("T") and are shown pushing on the normal splenic tissue, a small bit of which is shown at the bottom right of Fig. 2*D* ("NS"). The tumor cells have coarsely chromatin (Fig. 2*D*, inset). Remarkably, the same spleen contained a focus of metastatic adenocarcinoma (data not shown). The finding of two instances of sharks with two cancers each (RTLA 7300 and 523) provides particularly strong evidence that sharks can be highly susceptible to cancer because the same finding in man or mouse point immediately to the possibility of a genetic susceptibility to cancer or high carcinogen exposure. Taken together, these cases establish the susceptibility of chondrichthyans to cancers.[4]

[4] A third, previously unreported RTLA tumor (case 6887) was potentially a fibroma from a tiger shark found in the Pacific Ocean near Hana, Maui County, Hawaii. It was whitish, sessile, fibrous, 16-cm mass on the dorsal surface of the head. Microscopically, the neoplasm consisted of sparsely cellular fibrous tissue (data not shown). It was not possible to determine whether invasion had occurred because none of the histologic sections included normal tissue. The surface of the neoplasm was more cellular than the more myxoid central parts of the tumor. The location of this benign, well-differentiated fibroma suggested dermal origin. The low cellularity of this tumor is similar to that of fibroma of mice and marine turtles.

Discussion

The evidence herein conclusively demonstrates that, as with other vertebrates, sharks and their relatives do develop both benign and malignant neoplasms. These tumors are analogous to their counterparts in other organisms, including bony fishes, rodents, and humans.

It is worth noting that neoplasms have also been reported in the more primitive cartilaginous jawless fishes. Examples of such neoplasms include a metastatic melanoma in a lamprey and an epizootic hepatocellular carcinoma in a hagfish, *Myxine glutinosa* (27). Likewise, neoplasms have been reported in a variety of evolutionarily advanced cartilaginous fishes such as lungfish, *Protopterus annectens* and *Protopterus aethiopicus* (28–30), paddlefish, *Polyodon spathula* (31), sturgeon, *Acipenser spathula* (32, 33), and bowfin, *Amia calva* (34). These are not all isolated cases, as indicated by epizootics of hepatocellular carcinoma in paddlefish from the Detroit River (35).

Shark Cancer Rates: Not Determined. Although shark cartilage distributors insist that sharks rarely get cancer, actual cancer rates in sharks have not been determined. Few neoplasms have been documented in chondrichthyans, possibly because, as primarily pelagic (open water) marine animals, they are exposed to a diluted level of environmental carcinogens (36). Consistent with this point is that tumors of pelagic bony fishes are as rare as those of chondrichthyans. In comparison, benthic (bottom-dwelling) bony fish that feed on the meiofauna of polluted waterways can have epizootic skin and liver neoplasms whose frequencies can exceed 50% (37, 38). In fact, of the ~150 reported epizootic neoplasms, all have occurred in fish from inland or coastal waters; none were from pelagic fish (*e.g.,* ref. 39).

The rare documentation of chondrichthyan neoplasms may also be due to the small number of tumors that reach investigators. Cancerous fish in open waters suffer from two synergistic disadvantages, including sparse shelter (seaweed, rocks, and/or coral) and the presence of large predators. Cancerous fish in open waters, including sharks, are thus more likely to be eaten by predators before being caught by man.

Perhaps the most compelling argument for the paucity of chondrichthyan neoplasms is that there have been no systematic tumor surveys of sharks. This is in sharp contrast to bony fishes, for which frequent tumor surveys have yielded the bulk of the known fish tumor cases (*e.g.,* ref. 39). The theory that many new chondrichthyan neoplasms would be found by systematic surveys is suggested by several examples: (*a*) James Johnstone, a Liverpool physician, solicited diseased specimens and reported four melanomas in a 3-year period; (*b*) the Maine Department of Natural Resources put out a call to fishermen for diseased specimens, yielding two neoplasms in spiny dogfish within a 6-month period; and (*c*) George Balazs of the National Marine Fisheries Service distributed a tumor solicitation form and received the tiger shark fibroma described in the present report. Beyond surveys, far fewer chondrichthyan specimens are available for examination from sportsmen and commercial fishermen compared with bony fish and shellfish. Neoplasia is commonly found among fish (39) and shellfish (40, 41) that have been methodically studied; this even holds true for other diverse invertebrates such as coral (42) and flatworms (36, 40). It is important that systematic surveys of shark cancer incidence be pursued. If tumor incidence in shark and other pelagic fish is indeed low, such studies would provide a baseline barometer for increases in cancer because of environmental contamination.

Finally, it remains possible that chondrichthyans have an innately low susceptibility to cancer. Such a finding could be due to a variety of factors relating to carcinogen metabolism or DNA repair. Differential susceptibility to carcinogens is well established in a broad spectrum of animal models, including certain species of fishes. For example, there is a high incidence of liver neoplasms among English sole, *Parophrys vetulus*, that reside in contaminated waterways in Puget Sound (43–45), whereas the incidence of liver tumors in starry flounder, *Platichthys stellatus*, from these same waters is comparatively low. The starry flounder is in the same family (Pleuronectidae) as the English sole, and the disparity in liver lesion incidences has been attributed to species-specific differences in hepatic xenobiotic-metabolizing enzymes (46). Differences in detoxification mechanisms that could contribute to low tumor prevalence have also been found among some chondrichthyans (47).

It has been argued that the failure to induce tumors in laboratory studies is additional evidence that sharks are resistant to tumors. In the primary study that forms the basis for these remarks, nurse sharks, *Ginglymostoma cirratum*, were fed maximum sublethal doses of aflatoxin B1 for up to 50 days without developing visible tumors (48). Concluding from this experiment that sharks are resistant to tumors is unjustified for two reasons. First, it is often difficult to optimize experimental carcinogenic protocols. For example, although English sole are highly susceptible to liver tumors in the wild, numerous efforts to establish tumors in laboratory studies by multiple investigators with a variety of protocols have proven unsuccessful. In addition, a 50-day postexposure period is not adequate for tumors to grow to detectable size in a cold-water species. Let us consider the most optimistic scenario in which a tumor is generated instantly upon carcinogen exposure. The doubling time of shark tumors, although not known, can be estimated from the temperature at which the sharks were kept (~21°C), the temperature at which mammalian cells grow (37°C), and the doubling time of mammalian cancers (25 hours). The temperature difference is ~16°C. We can expect that each 10°C temperature difference corresponds to a 2 to 3-fold difference in reaction rate (49), and a 16°C difference could result in about a 4-fold difference in cell division rate or ~100 hours. As such, a tumor mass would only reach a diameter of 0.16 mm in 50 days, too small to be obvious to the naked eye. The negative result in this experiment is therefore meaningless. We conclude that cancer incidence in sharks is impossible to establish based on present data and that there is no evidence that sharks are any less susceptible to cancer than bony fish from the same open ocean environment.

Even if Sharks Were Less Susceptible to Cancer. Even if sharks did show unusually low susceptibility to cancer compared with other organisms, this would not support the use of crude cartilage extracts to treat cancer. We know, for example, that there are bacterial proteins that allow other proteins to function in boiling hot environments (50). Does this mean that we should expect to survive in boiling water after eating crude extracts of those bacteria? Obviously, no. Those proteins would likely be cut into useless fragments by our digestive enzymes or denatured by the acidic environment of the stomach before entering our cells. Even if sharks were to show low susceptibility to cancer, we would need to know whether it is because of decreased exposure to carcinogens, increased immunity against cancer after it arises, or the presence of metabolic pathways that either decrease conversion of mutagens into their active forms or promote more efficient repair of DNA. Learning that a low susceptibility is due to low carcinogen exposure would not be new. Also, if the immunity of sharks to cancer is high, there is little hope of acquiring that immunity through ingestion of cartilage. If metabolic or repair pathways are different, who is to say whether sharks are exposed to the same mutagens as humans, or whether their set of metabolic pathways might be even less competent than ours in dealing with our mutagens? In conclusion, even if sharks are less susceptible to cancer, it is illogical to conclude that crude extracts of shark cartilage would be successful in curing cancer in humans.

Shark Cartilage Contains Substances That Inhibit Tumor Angiogenesis and Invasion. Although its raw consumption is useless, cartilage contains substances that may be used against cancer. More than 30 years ago, Folkman (3) proposed that tumorigenesis could be inhibited, blocked, or even reversed by inhibiting angiogenesis. He also concluded that without neovascularization to provide nutrients, allow gas exchange, and remove wastes, tumors stop growing at a diameter of 0.5 to 1 mm (2). Since that time, antiangiogenic factors have been isolated from various sources, including cartilage from calves (4) and sharks (5). Similarly, it has been long observed that human cancer rarely invades cartilage (51). Some investigators attribute this phenomenon to the presence of collagenase inhibitors found in cartilage that have been found to inhibit invasion by cancer cells (52). Less interesting alternative explanations for rare lack of invasion of cartilage are its hardness (poor permeability of a solid matrix to cells) and the possibility that the low vascularity of cartilage makes it a less hospitable environment for growth of cancer cells and, in particular, the vascular tissue required for tumor growth.

The next logical steps in developing these anticancer components into modes of cancer therapy involve identification, purification, and characterization of these substances. The important questions to answer include: What are the key characteristics of these substances that cause their action? What are their potential toxicities? What are their effective routes of administration? What is the effectiveness of reaching the target tissue in any amount? What are their concentrations? What cancers are most effectively treated? Lane and others ignore these critical steps and suggest that consuming crude cartilage extracts by mouth or rectum can be curative of all cancers. It is notable that despite more than a decade of evaluation of shark cartilage, not a single controlled study has established any efficacy of crude cartilage extracts against cancer (6, 53).

Still Hope for Cancer Inhibitors. Despite the above arguments, it is possible that highly purified components of cartilage, including those from shark cartilage, may hold some benefit for the treatment of human cancers.

For example, squalamine, which is derived from stomach and liver of the dogfish shark, inhibited angiogenesis and solid tumor growth *in vivo* in phase I clinical trials that were initiated to evaluate the feasibility of this novel aminosterol for cancer treatment (54). This approach of carefully evaluating and testing components of cartilage or other tissues may ultimately prove beneficial. It should be noted that when unique, therapeutically valuable compounds are identified in any biological material, those compounds can be chemically synthesized or produced in microorganisms to avoid endangerment of species.

What Broader Lessons? The evidence of shark cancer presented here and discussion of the illogic behind the pursuit of shark cartilage therapies have implications beyond the reduction of shark populations and the misdirection of patients to ineffective cancer therapies. The successful sale of crude shark cartilage to the public represents a failure of our society to deal with pseudoscience. The stark contrast between the rigor of scientific peer review and the lack of any substantive review in the popular press underscores the failure of our educational and journalistic systems to ingrain the value of intellectual honesty or to promote the ability of the media and the public to think critically. The increased power of electronic media has increased the potential harm of pseudoscience, turning what would otherwise be quaint cultural curiosities into potentially serious societal and ecological problems. The growing power of our technologies and astoundingly effective means of electronic communication make it increasingly important to minimize the dangers of those technologies. Minimizing these dangers demands new competencies for societal leaders in scientific reasoning. Jean-Jacques Rousseau was not without merit when he argued in his 1750 prize-winning essay that science has a corrupting influence on society (55). Leaders in the scientific community have noted the need for effective communication between scientists and the public to counteract the tendency of overregulation caused by sensationalized discussions of issues such as cloning and bioterrorism (56, 57). Only through a reliance on reason will it be possible to fulfill the Baconian ideal of science for the benefit of man (58) without harming society or, at worst, destroying the ecosystem upon which life depends (59).

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Appendix

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