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ON THE HUNT FOR CANCER'S MICROBIAL "PARTY" IN THE ANIMAL KINGDOM

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YOUNG REVIEWERS:

ARYAN
AGE: 13

EMILY
AGE: 14

EMMA
AGE: 10

Did you know that food, microbes, and cancer are often linked together? These links are well-studied in humans, but not as well-studied in other species. We wanted to find out whether specific foods and/or microbes are linked with cancer across non-human species. So, we searched over a thousand articles reporting links between diet, microbes, and cancer. We found that some microbes, such as *Helicobacter,* papillomaviruses, and *Fusobacteria* which are often found in carnivores, can promote tumor development in people as well as in other animals. Other microbes, such as the *Lactobacillus* found in milk products, can decrease tumor development in people and other animals. There is lots more to learn about these patterns across hundreds of species. Ultimately, these results have great potential to help researchers understand the variation in cancer

risk across animals, and to help doctors and vets improve the early detection and treatment of cancer.

MICROBES

Tiny organisms, such as bacteria and amoebae, that can be found inside and outside other organisms.

MICROBIOME

A group of microorganisms living in a specific environment.

CANCER-INDUCING MICROBES

Microbes that increase the risk of developing cancer.

ONCOBIOME

The collection of all cancer-inducing microbes in an animal.

CANCER-PROTECTIVE MICROBES

Microbes that decrease the risk of developing cancer.

GUT MICROBES CAN AFFECT CANCER PROGRESSION

Did you know that there are trillions of **microbes** that live in our guts? They come from the things we eat and the people, animals, or objects we are exposed to during our lives. These microbes have been a part of human bodies since humans first evolved, and they affect multiple aspects of our existence. Together, all of an animal's microbes are called its **microbiome**

One of the things microbes affect is the development of cancer and how it progresses as time goes on. There are **cancer-inducing microbes** that help cancer grow. Cancer-inducing microbes form a collection referred to as the **oncobiome**. These cancer-causing microbes are partly responsible for inducing cancer in 2.2 million people every year. On the bright side, there are also **cancer-protective microbes** that help our bodies fight cancer and reduce the risk of getting it in the first place. These microbes usually come from healthy diets.

SEARCHING THE SCIENTIFIC LITERATURE

We looked for articles in the literature referring to associations between diet, microbes, and cancer in non-human animals. To find these articles, we used keywords and synonyms related to diet, microbes, the gut, cancer, and species. We also used specific keywords to specify that we wanted to exclude studies that focused on humans. We excluded those articles because there have been many discoveries on the associations between diet, microbes, and cancer in humans, but the new aspect of our research is that it is focused on non-human animals. We typed these keywords and synonyms into the Arizona State University library search engine and, after several rounds of reading and excluding irrelevant articles, we ended up with 31 relevant articles [1]. From these 31 articles, we collected information about the standard diet of the animal(s), the way the microbes were added to the animals (with experimental tools or naturally found in the animals), the type of animal used in the experiment, and the effects of diet and/or microbes on cancer in these animals (Figure 1).

In general, we found that most of the articles described experiments in rodents, such as mice and rats. In most cases, the researchers experimentally inserted microbes through the mouths of these animals, and most of the researchers studied the effect of these microbes on cancers of the gut.

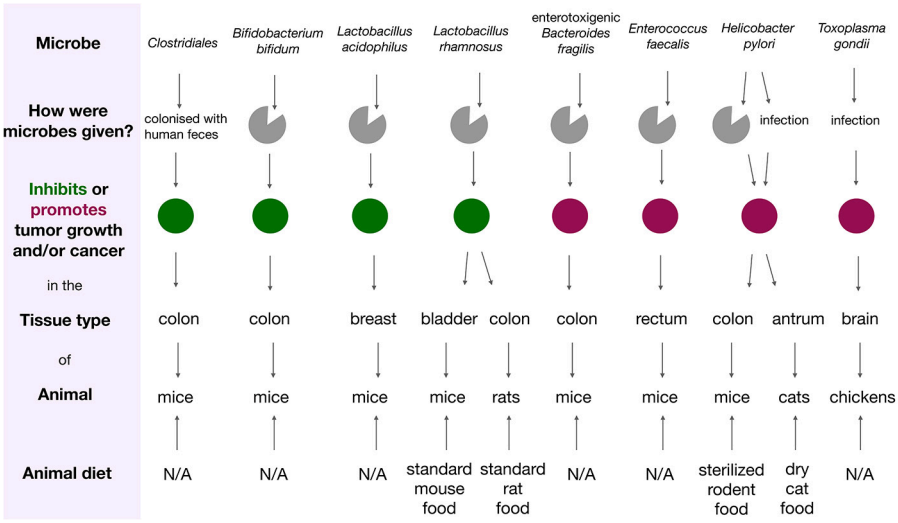

Figure 1

Examples of microbes that promote or inhibit tumor (and/or cancer) development in non-human animals. The Pac-Man image shows that the microbes were inserted through the mouth of the animal. The antrum is part of the stomach. N/A refers to information not being available. Table adapted from [1].

LACTOBACILLI: MICROBES THAT HELP FIGHT CANCER

Some of the microbes that make up the microbiome fight cancer and protect the organism they live in. These cancer-protective microbes fight cancer by performing actions like preventing **tumors** from forming, reducing tumor size, and preventing cancer from spreading (a process called **metastasis**). One of these cancer-fighting microbes is called *Lactobacillus*, and it is mostly found in dairy products such as milk and cheese. Studies have found that *Lactobacillus* helps prevent breast cancer in mice by stopping the formation of tumors and cancer cells. It is incredible that microbes from the foods animals eat can help their bodies stay healthy in such microscopic yet remarkable ways.

TUMOR

A mass of abnormally dividing cells.

METASTASIS

The spread of cancer cells to other parts of the body.

MICROBES THAT CONTRIBUTE TO CANCER

Some microbes seem to be associated with cancer not only in people, but in other animals as well. For example, particles over a million times smaller than the tip of a human finger, such as papillomaviruses, are associated with skin cancer in people and dogs. These viruses enter animal cells and can damage the cellular machinery that fixes DNA damage and/or controls the cells' response to stress. Two types of bacteria, *Bacteroides fragilis* and *Fusobacterium nucleatum*, are also associated with cancer in people and mice. These microbes produce **toxins** that can damage the DNA, changing the way the cells connect to neighboring cells. This change in the way cells attach may trigger the metastasis of cancer cells to other parts of the body. Another bacterium, *Helicobacter*, is associated with cancer development in humans, mice, gerbils, and cats. *Helicobacter* leading to cell death, and the remaining gut cells adapt by dividing more. These microbes also produce toxins that increase the risk of these animals developing

TOXINS

Chemicals that are produced by living organisms and can cause damage to other organisms.

cancer in the gut. Given that *Helicobacter* bacteria are associated with cancer in both a predator (cat) and its prey (mouse), it could be interesting to test whether these germs are transmitted from prey to predator.

The germs associated with cancers in various animals may actually come from their diets. It seems that a group of meat-eating species (Carnivora) have a higher prevalence of tumors than other groups of mammals that eat mostly plants [2–4]. This is also true when we compare feeding levels on the food pyramid [5] (Figure 2). Could certain cancer-associated microbes thrive in specific diets? We do not know for sure yet whether this is true across species, but there is evidence that the microbes *Fusobacteria* and *Peptostreptococcus* are associated with tumor formation in humans and mice, and these germs are most often found in animals that eat meat [1].

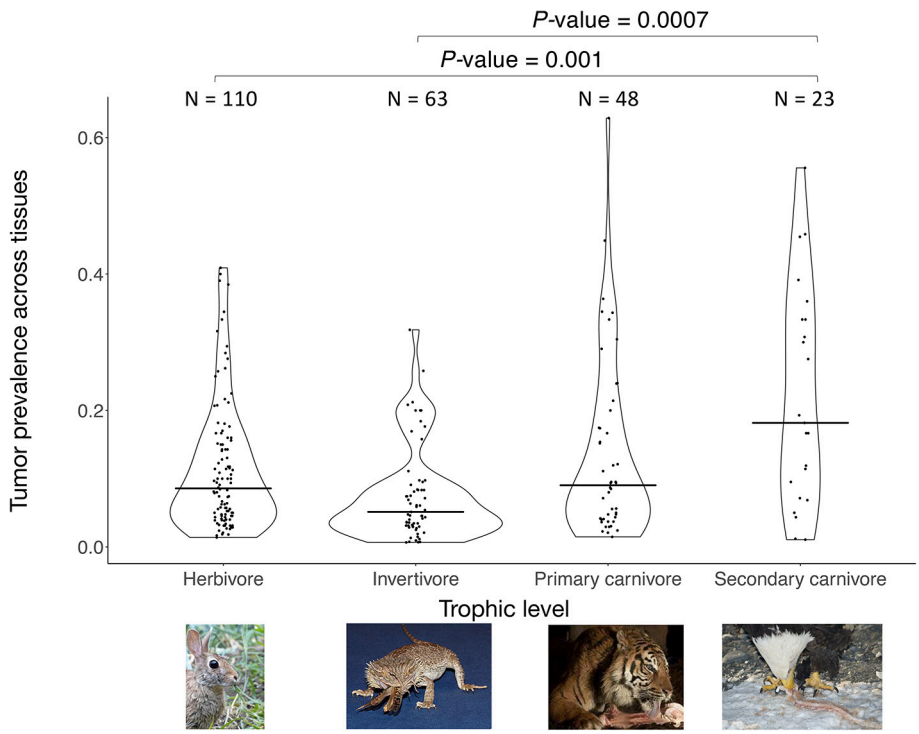

Figure 2

Figure 2

The prevalence of tumors across tissues is higher in animals of higher trophic (feeding) levels. For example, secondary carnivores have higher tumor prevalence than plant-eating animals (herbivores) and boneless-eating animals (invertivores). The *P*-value shows the feeding categories that are significantly different in their tumor prevalence. *N* shows the number of dots (i.e., species) in each feeding category, and the horizontal lines show the median number of tumor prevalence in each feeding category. Images show representative species (rabbit, bearded dragon, tiger, and bald eagle) in each feeding category. Images are from Wikimedia Commons. Figure adapted from [5].

Sometimes the development of cancer might not be related to *specific* microbes, but might have to do with the **diversity** of microbes. Macaques and humans that ate a Western-type diet (which consists of a lot of red/processed meat, fried foods, butter, eggs, refined sugars, and salt, and is associated with cancer) had a lower diversity of microbes compared to macaques and humans that ate a Mediterranean-type diet (consisting of many plant-based products) [1].

DIVERSITY

Consisting of a variety of different elements.

THE EFFECTS OF MICROBES ON CANCER ARE COMPLEX

Microbes such as *Bacteroides* and *Clostridium* have been found to have both cancer-protective and cancer-inducing effects. These microbes can either promote or protect from gut cancer (colorectal cancer) and skin cancer (melanoma), depending on an animal's genetic background and the type of food it eats. The genetic backgrounds of laboratory mice are very well-characterized, and each background has a separate name. For example, *Clostridium* promotes tumor formation in the guts of mice with a genetic background called FVB/N, whereas the same microbe inhibits the growth of colorectal cancer cells and melanoma cells in mice with a C57BL/6 genetic background. In terms of diet, *Bacteroides* can cause tumor formation in the guts of mice, but may also protect them from cancer if the mice have eaten foods that contain soluble fiber, which has anti-inflammatory properties [1].

A SURVIVAL GAME BETWEEN THREE PLAYERS

There are three different players in cancer formation: the animal, the microbes, and the cancer cells. First, animals rarely benefit from having cancer. Second, certain microbes can gain a survival and reproductive advantage from using some of the resources that cancer cells tend to hoard, like cell-free DNA. The benefit that microbes can attain from cancer cells varies based on the function of the microbes. Third, the cancer cells benefit from interacting with *Helicobacter pylori* as this microbe promotes cancer in the stomach. As *H. pylori* attaches to animal cells and divides, it also triggers those cells to divide. The cancer cells are a burden to the animal, since they develop the ability to steal more resources from the body and migrate to different organs and tissues when they use up the resources from one place [6].

CONCLUSION

In humans, cancer kills almost 10 million people every year. Some microbes, such as the *Lactobacillus* often found in milk products, are beneficial in terms of lowering the chances of tumor formation in people and other animals, whereas other microbes, such as the papillomaviruses, *Helicobacter*, and *Fusobacteria* often found in meat-eating species, have the opposite effect and often increase the likelihood of tumor formation. Although these links between diet, microbes, and cancer are only known for a few animals so far, we hope that future studies will find such links across many more animal species. This can be a difficult task given the complexity of the microbiome in the gut; the interactions of these microbes with the animals' genes, age, sex, and environment; and the difficulty of growing and studying almost 99% of these microbes in the lab. Many

of these problems can potentially be solved with recent technological advances that allow the analysis of thousands of gut microbes from fecal (poop) samples, for example.

Understanding the links between food, microbes, and cancer across species may improve the ways medical doctors and vets detect and treat cancers. For example, healthcare providers may be able to adjust an animal's food, track the presence of potentially harmful microbes in its body, and potentially transplant cancer-protective microbes into the gut. Together, such therapies could be life-saving for many animals suffering from cancer.

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ORIGINAL SOURCE ARTICLE

Kapsetaki, S. E., Marquez Alcaraz, G., Maley, C. C., Whisner, C. M., and Aktipis, A. 2022. Diet, microbes, and cancer across the tree of life: A systematic review. *Curr. Nutr. Rep.* 11:508–25. doi: 10.1007/s13668-022-00420-5

REFERENCES

1. Kapsetaki, S. E., Marquez Alcaraz, G., Maley, C. C., Whisner, C. M., and Aktipis, A. 2022. Diet, microbes, and cancer across the tree of life: A systematic review. *Curr. Nutr. Rep.* 11:508–25. doi: 10.1007/s13668-022-00420-5
2. Madsen, T., Arnal, A., Vittecoq, M., Bernex, F., Abadie, J., Labrut, S., et al. 2017. "Chapter 2—Cancer prevalence and etiology in wild and captive animals," in *Ecology and Evolution of Cancer*, eds B. Ujvari, B. Roche, F. Thomas (Cambridge, MA: Academic Press), 11–46. doi: 10.1016/B978-0-12-804310-3.00002-8
3. Lombard, L. S., and Witte, E. J. 1959. Frequency and types of tumors in mammals and birds of the Philadelphia Zoological Garden. *Cancer Res.* 19:127–41.
4. Vincze, O., Colchero, F., Lemaître, J. F., Conde, D. A., Pavard, S., Bieuville, M., et al. 2021. Cancer risk across mammals. *Nature* 601:263–7. doi: 10.1038/s41586-021-04224-5
5. Kapsetaki, S. E., Compton, Z., Rupp, S. M., Garner, M. M., Duke, E. G., Boddy, A. M., et al. 2022. The ecology of cancer prevalence across species: Cancer prevalence is highest in desert species and high trophic levels. *BioRxiv* 2022.08.23.504890. doi: 10.1101/2022.08.23.504890
6. Aktipis, A. 2020. *The Cheating Cell: How Evolution Helps Us Understand and Treat Cancer*. Available online at: https://books.google.ca/books?hl=en&lr=&id=ASOyDwAAQBAJ&oi=fnd&pg=PR9&ots=4nsR4qd4dp&sig=4BxAtYorcmn4FZF4gzWqrTodcYo (accessed June 1, 2022).

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CONFLICT OF INTEREST: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

YOUNG REVIEWERS

ARYAN, AGE: 13
Hi, My name is Aryan. In the Scientific fields, I am interested in astronomy and physics. I had some activities and studies in these fields. Recently, in biotechnology and bioengineering, I have been interested in applying mathematics and technology in biology. I love the Science fiction novels like the Dune Novels.

EMILY, AGE: 14
My name is Emily. I am 14 years old. I enjoy family trips to the beach, fishing, and canoeing. At school my favorite subjects are mathematics and science. I spend my spare time working out at the gym.

EMMA, AGE: 10
My name is Emma. I am a fifth grader. I love to read and I love doing experiments in my spare time. I enjoy going to the beach and exploring nature. Fun fact about me is that I collect rocks and I have over 200 unique rocks in my collection. Whenever I have extra time I sketch movie characters.

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