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Gut cancer increases the risk of *Drosophila* being preyed upon by hunting spiders

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Predators are thought to prey on individuals that are in poor physical condition, although the evidence supporting this is ambiguous. We tested whether sick individuals were more predated using *Drosophila melanogaster* flies as manipulable prey. We asked whether hunting spiders, trapped from the wild, would selectively prey upon flies with compromised health (i.e. chronically infected or cancerous) versus healthy flies, under laboratory conditions. Flies chronically infected with the bacterium *Providencia rettgeri*, a natural *Drosophila* pathogen, were not selectively preyed upon by jumping spiders. We strengthened and confirmed our finding with another hunting spider species, small wolf spiders. This result supports the hypothesis that chronic infection is associated with reduced symptoms notably to avoid the potentially deadly consequences for pathogens of host predation. We then induced colon cancer in some of the flies and asked whether the presence of cancer led to selective predation; there is little empirical evidence for this, even in vertebrates. As the cancer developed, the incidence of predation by jumping spiders on the afflicted flies increased. We conclude that disease can have different lethal consequences through predation, even in invertebrate species, and that cancer is a factor in selective predation. Our results may explain why early tumours, but not metastasized cancers, are commonly detected in organisms in the wild, as cancer-bearing individuals are rapidly eliminated due to the strong selective pressure against them.

In vertebrates, individuals that are injured or diseased are often preyed upon, as are juveniles that have not reached adult speed or reflex (Furey et al., 2021; Genovart et al., 2010; Mesa, Poe, Gadomski, & Petersen, 1994; Møller, 2008; Murray, 2002). This is especially true when a predator's preferred type of prey is difficult to catch at the prime of its performance (Temple, 1987); however, there are exceptions (Penteriani et al., 2008). Although this conventional wisdom of selective predation on substandard individuals is largely accepted, only a few studies have tested it empirically. Selective predation can only be said to exist when the relative frequencies of the types of prey in a predator's diet differ from the frequencies in the environment (Chesson, 1978). Hence, to test the selective prey hypothesis in the wild, data on the types of prey sought by predators and the health status of the whole prey population would need to be determined. Although understanding the effect of selective predation may be vitally important in the context of eco-evolutionary dynamics (Brunner, Anaya-Rojas, Matthews, & Eizaguirre, 2017; Brunner, Deere, Egas, Eizaguirre, & Raeymaekers, 2019), these data are difficult to obtain and the topic has been subject more to speculation than to empirical study.

Probably the most well-studied question regarding selective predation is whether predators prey more on individuals in suboptimal condition than on healthy individuals. Despite the prediction that predators will avoid infected prey to avoid the risk of getting sick themselves (Goren & Ben-Ami, 2017), field observations suggest that infections could increase the vulnerability of prey to predation (Adelman, Mayer, & Hawley, 2017; Duffy, Hall, Tessier, & Huebner, 2005; Gooding et al., 2020; Miller et al., 2008; Moller & Erritzoe, 2000; Moller, Erritzoe, & Tottrup, 2010; Møller & Nielsen, 2007; Murray, Cary, & Keith, 2006) and there is some experimental support for this (DeBlieux & Hoverman, 2019; Gallagher et al., 2019; Johnson, Stanton, Preu, Forshay, & Carpenter, 2006; Murray, 2002). Consequently, by mediating selective predation, parasites can mediate the relationship between hosts and their prey (Hall, Cáceres, Duffy, & Cáceres, 2005; Møller, 2008). For instance, removing predators can reduce vertebrate prey populations (Sih, Crowley, Mcpeek, Petranka, & Strohmeier, 1985), which seems counterintuitive, as predators are expected to remove prey. However, mathematical models predict that virulent parasites will be selected against if predation disproportionately removes them

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before they can be transmitted to the next host (Packer, Holt, Hudson, Lafferty, & Dobson, 2003). Without this check on virulent parasites by the predator, more prey may die from lethal infections than from predation. Hence, if selective predation for infected individuals is a common pattern, it may also be a major driver of host and parasite evolution and can no longer be ignored (Møller, 2008).

It is also relevant to consider that noninfectious diseases could also increase the risk of being predated. In fact, understanding the role of cancer in ecosystem function has been identified as a key endeavour (Dujon, Aktipis, et al., 2021). So far, most of our knowledge is based on the consequence of transmissible cancer for an apex predator (i.e. Tasmanian devil, *Sarcophilus harrisii*, Cunningham, Johnson, & Jones, 2020; Hollings, Jones, Mooney, & McCallum, 2014; Hollings, Jones, Mooney, & McCallum, 2016; Woods et al., 2018), and little to nothing is known about the potential selective predation of prey that are sick due to a noninfectious disease (see Perret, Gidoin, Ujvari, Thomas, & Roche, 2020 for a theoretical study). Mutations can occur during cell replication and division required to grow and maintain multicellular animals, and certain types of mutation, said oncogenic mutations, can lead to the formation of tumours (Aktipis et al., 2015; Albuquerque, Drummond do Val, Doherty, & de Magalhães, 2018; Hanahan & Weinberg, 2011; National Cancer Institute, 2020a). In most cases, tumours are benign (Bissell & Hines, 2011), but they can be malignant, and even fatal (Aktipis et al., 2015; Albuquerque et al., 2018; Hanahan & Weinberg, 2011; National Cancer Institute, 2020b). Clinical categorization of tumours has been established in unchallenging, 'benign' environments (i.e. in the laboratory or clinic), usually to the point of death via organ failure. The impact of tumour progression is likely to strongly influence an individual's life history traits (e.g. life span and reproductive output but also competitive and dispersal ability and pathogen susceptibility); yet, its impact under more natural conditions has largely been ignored (Roche, Møller, DeGregori, & Thomas, 2017; Vittecoq et al., 2013). Furthermore, depending on the relationship between tumour development and the health of the prey, predation could affect the selection of oncogenic mutations and thus the risk of developing cancer. To our knowledge, the possible interactions between a predator and a prey that is afflicted with cancer are poorly understood and have not been empirically studied (Vittecoq et al., 2013).

Here, we induced chronic bacterial infection and colon cancer in prey to understand their role in increasing the likelihood of being predated. We used the fruit fly *Drosophila melanogaster*, a genetically tractable model organism which has recently been used to study the effect of cancer from an ecological perspective (Arnal et al., 2017; Dawson et al., 2018) and is already a well-characterized model for infectious and noninfectious diseases, as a novel model for sick prey. We assessed the predation of flies by hunting spiders, using flies that were either chronically infected by a wild-caught bacterial pathogen (*Providencia rettgeri*) or had genetically induced intestinal cancer, under laboratory-controlled conditions. These conditions allowed for the ideal experimental setting to study predation and the role of prey wellbeing in a population context.

METHODS

Prey and Predators

We used only male *D. melanogaster* as prey in this study to avoid sex effects. Bacterial cultures were grown to saturation overnight at 37 °C in LB liquid medium (LB broth, Miller, VWR, Lutterworth, U.K.). Saturated cultures were suspended and diluted in phosphate buffered saline (PBS, pH 7.4). We induced chronic infection by injecting 23 nl of a suspension containing between 1500 and 2500 cells of the bacterium *P. rettgeri* (strain *Dmel*, isolated from wild-caught *D. melanogaster*; Juneja & Lazzaro, 2009) in PBS into the abdomen of flies (Canton S line, a wildtype genotype kept in the laboratory for several decades). The same volume of sterile PBS without bacteria was injected into another group of flies that served as the control. Individuals surviving for 3 days or more after injection of the bacteria have an established chronic infection, as we have previously demonstrated (Duneau et al., 2017), and their immune response was expected to be activated (Chambers, Jacobson, Khalil, & Lazzaro, 2019). To induce tumours in the flies, we manipulated signalling pathways that regulate cell growth in mammals, which have a conserved function in *Drosophila*, the EGFR and Wnt pathways (Millburn et al., 2016; Mirzoyan et al., 2019; Rudrapatna, Cagan, & Das, 2012; Villegas, 2019). We used targeted induction of these pathways (Rasv12 for EGFR, APC RNAi for the Wnt pathway) to induce two types of pathology in the intestinal epithelium (i.e. hyperplasia, sometimes referred to as benign tumour, and cancer; hyperplasia is the enlargement of an organ or tissue caused by increased cell division and is often an initial stage in the development of cancer). These types of genetically induced intestinal cancers are appropriate for this study, as they do not overtly affect physical performance including locomotion, and thus allow for the study of the interaction of oncogenic phenomena and predation (see Dawson et al., 2018 for locomotion assays in gut cancerous flies in another genetic background). To generate tumours in the gut of *Drosophila*, flies esg^{TS} (*esgGal4*, $Gal80^{ts}$, *UAS-GFP*) were crossed to either RNAi TRiP library background control flies from the Bloomington Drosophila Resource Center, BDRC (BDRC TriP library 35786), flies carrying a $UAS\text{-}Ras^{v12}$ (BDRC 64196) or flies carrying a combination of $UAS\text{-}Ras^{v12}$ (BDRC 641926) and *UAS-APC-RNAi* (BDRC TriP library 28582) combined. The expression of Ras^{v12} in progenitor cells stimulates an accelerated division of intestinal stem cells (ISCs) and a low level of epithelial disorganization in the gut, akin to a dysplastic tissue (Buchon, Broderick, Kuraishi, & Lemaitre, 2010; Houtz, Bonfini, Bing, & Buchon, 2019; also referred to below as hyperplasia). The overexpression of Ras^{v12} combined with the knock-down of *APC* leads to increased ISC proliferation, and an accumulation of progenitor cells and unpolarized epithelial cells in the gut, reminiscent of an intestinal disseminated tumour (Wang et al., 2013; also referred to below as cancerous). F1 flies from these crosses were raised at 18 °C (Gal4 off, transgene expression off, normal development and emergence), and 3 days after emergence were switched to 29 °C (Gal4 on, transgene expression on) for 10 or 20 days before being used in the experiment. As in Wang et al. (2013), crosses with WT flies showed mild tissue renewal (restricted GFP signal), flies expressing Ras^{v12} showed disseminated GFP in their gut and flies expressing Ras^{v12} and *APC RNAi* showed gut enlargement and GFP accumulation. The longer the induction is done, the stronger is the phenotype, leading to a gradient from induced hyperplasia after 10 days (i.e. mild colon enlargement) to induced cancer after 20 days (i.e. large tumours that invade the intestinal lumen).

We used two families of hunting spiders as predators: jumping spiders of several species from the family Salticidae (see Fig. 1) and small wolf spiders from the family Lycosidae (probably *Pardosa lugubris*), both of which hunt by wandering rather than by using webs as traps. Both types of spider have already successfully been used to test for selective predation (Holmberg & Turnbull, 1982; Vickers & Taylor, 2018).

All spiders in the study were obtained from the wild during their daily activity and were therefore of different age, sex, size and level of satiety. We therefore did not test how specific characteristics of the predator affected our results. Every spider caught was used and each was randomly assigned in the different experiments/trials. We

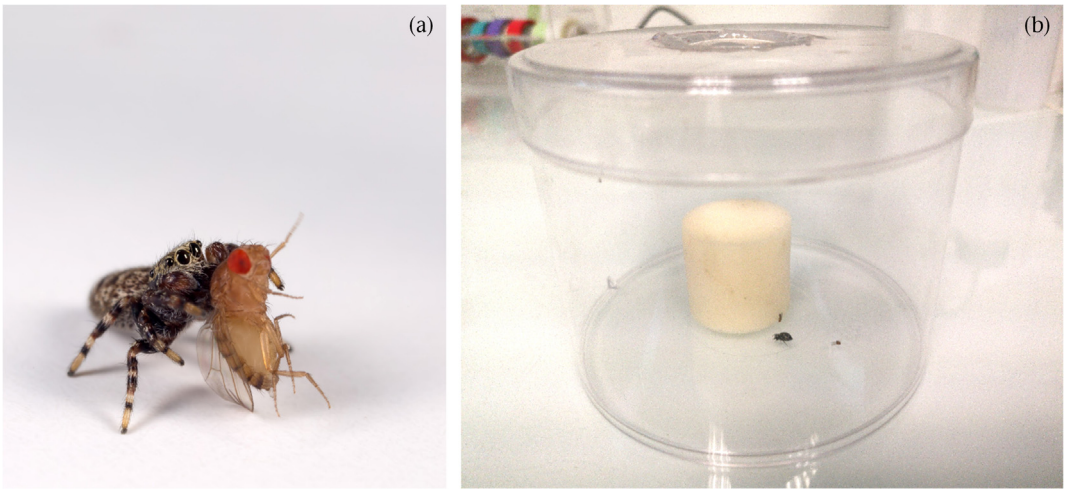

Figure 1. Photograph of (a) a jumping spider consuming a female *Drosophila melanogaster* to illustrate the predatory behaviour in the laboratory and (b) an arena used for the assays.

kept them individually for less than a week in the same box type as the type used for the trial. They were fed daily with healthy *Drosophila*. Spiders used for testing the effect of cancer were sampled and tested on the Cornell University campus (Ithaca, NY, U.S.A.) and those used for testing the effect of infectious diseases were sampled and tested on the campus of the University of Toulouse 3 (Toulouse, France). Jumping spider species differ between the American and European continents. In this study, we used species from both Europe and America to test the effect of infectious disease and of cancer, respectively. While the species differed, we did not observe differences that lead us to believe this introduces a bias that would affect our conclusions.

Jumping spiders have the sharpest vision of any arthropod, even surpassing that of many vertebrates (Land & Nilsson, 2012). They hunt during the day and rely on this astonishing vision when catching prey. Similar to the way a cat stalks its prey, jumping spiders turn towards their prey, directed by a pair of lateral eyes that provide a nearly panoramic field of view with the ability to discern motion (Zurek & Nelson, 2012). Then, the spiders track, approach and jump on the prey. The vision accuracy is conferred by two pairs of forward-facing eyes that also provide a precise perception of depth (Nagata et al., 2012; Zurek, Taylor, Evans, & Nelson, 2010). Jumping spiders are sensitive to UV and UV-induced fluorescence, notably for courtship behaviour (Lim, Land, & Li, 2007). As we revealed the presence of hyperplasia/tumours by scoring the presence of GFP in the gut of the prey, one could wonder whether jumping spiders prefer to prey upon fluorescent *Drosophila*. However, in this case, the GFP was only visible after dissection of the gut and under a fluorescence microscope when the cells were excited with a laser of a specific wavelength (488 nm). Therefore, cancerous and healthy prey did not differ by visible GFP during the experiment.

We next wanted to test whether compromised individuals would be more likely to be eaten by another type of hunting spider with a different hunting behaviour, wolf spiders. This was additionally performed to strengthen our finding that chronic infection does not affect predation. Wolf spiders are generally nocturnal hunters and their eyes function mainly as low-light movement detectors; however, *Pardosa* species mostly hunt during the day (Edgar, 1969). Their vision is not as acute as that of jumping spiders (Land & Nilsson, 2012). The use of visual cues in prey detection and orientation have only been well studied in jumping spiders, and empirical evidence suggests that wolf spiders rely more on vibrations than on vision to capture their prey (Lizotte & Rovner, 1988). Hence, the differences between these two types of hunting spiders primarily lie in their ability to prey on flies that are at rest. In an environment where there is no place to hide, jumping spiders would likely prey equally well on moving and nonmoving prey, and selective predation in this case should depend largely on the prey's capacity to escape.

Predation Trials

Predation trials were performed during the day by incubating five healthy and five sick flies, age-matched (5–9 days old), at 20 °C with a spider in a round plastic box (11.5 cm × 8.5 cm, Fig. 1b) containing a piece of wet cotton or foam. No spiders were starved before the experiment. The flies were first added to the box to settle before the introduction of the predators. After about 30 min, spiders were put in the box. The trials lasted for 4 h or when 50% of the flies had been preyed upon. Some spiders ate faster than expected and more than 50% of the prey were eaten in some trials. Individual spiders were never used twice as predators within an experiment.

To determine the number of surviving flies that were infected, we killed the remaining flies at the end of the predation period by grinding them in 250 μl of Luria-Bertani (LB) medium. A droplet of 5 μl of the resulting suspension was spread on a petri dish filled with agar containing LB medium, and the plates were incubated overnight at 37 °C to assess the presence of *P. rettgeri*. We calculated the proportion of infected flies at the end of the predation period by determining the number of droplets in which *P. rettgeri* were present. We performed the same process with infected and healthy flies but without predatory spiders to confirm that we could recover the expected 1:1 ratio of each treatment.

The number of surviving flies that had cancer were counted by dissecting all surviving flies and observing their guts under a fluorescent microscope, revealing the presence/absence of cancer, from which we could calculate the state of those that had been predated. Our protocol consistently led to tumour induction, although note that tumour size varies between individuals which could be a source of variation in our trials. In the unlikely event that some individuals considered to be carrying a tumour had a relatively small one, these individuals would be predated like control individuals.

Consequently, this would reduce the chance of statistically detecting an effect of the tumour on the risk of predation.

Statistical Analysis

Statistical analysis was performed using R version 4.1 (R Core Team, 2020). The use of the Fisher exact test or a chi-square test would have permitted us to test for every trial regardless of whether the number of flies from a particular category was more, or less, preyed upon than those from another category. However, we used a hypergeometric distribution instead of a chi-square distribution because, as flies were preyed upon, the population size decreased, and we only had information on predation rate per treatment at the end of the experiment. The *P* values for the experimental trials were summed and compared to the summed *P* value obtained by simulating random trials. We assessed the overall *P* value by determining the number of simulated trials required to have an observed result (summed *P* value observed) as probable as the simulation (summed *P* value simulated). Hence, a *P* value of 0.05 indicated that 20 trials would be sufficient to have the same result as the empirical data by chance, whereas a *P* value of 0.0001 meant that 10 000 trials would be required to achieve the same result as the empirical data by chance.

We used the Manly alpha index as the preference index to illustrate the selective predation on sick individuals (index 0: preference for healthy individuals; index 0.5: no preference; index 1: preference for sick individuals). It was calculated as log (total flies sick/flies sick but not eaten)/[log (total flies sick/flies sick but not eaten) + log (total flies healthy/flies healthy but not eaten)] as established by Manly (1972). The index was replaced by its limit when the total of non-eaten flies (either sick or healthy) was 0. Its value then became 1 if all sick flies were eaten or 0 if all healthy flies were eaten. We observed no cases where all flies, sick or healthy, were eaten, which would have led to an undetermined index value. To test whether the preference index for sick individuals increased with the severity of the cancer, we considered hyperplasia after 10 and 20 days of induction and cancer after 10 days and 20 days as ordinal variables. This was used because although we knew the rank of severity (i.e. from inducing hyperplasia for 10 days to inducing cancer for 20 days), we could not know the size of the differences between them. This allowed us to test in a single model (i.e. using an ordinal logistic regression) for the increase of the preference index with the increase in cancer severity.

Ethical Note

This study was carried out in accordance with all relevant animal welfare guidelines for invertebrates. Flies were infected while being anaesthetized with CO_2. At the end of the experiments, spiders were euthanized at −20 °C. Given the number of spiders used in this study, it is unlikely that our sampling had any impact on the natural populations.

RESULTS

Predation of Chronically Infected Flies

We tested whether chronic infection of male flies by *P. rettgeri* affected the risk of being preyed upon by spiders. Despite using two predator species, we did not detect selective predation on infected individuals by either type of hunting spider (Fig. 2).

Predation of Flies with Cancer

We asked whether cancer of the gut, which we induced, affected the risk of predation of male flies by hunting spiders. In one set of flies (esgts > UAS-Rasv12) we induced hyperplasia (the enlargement of an organ or tissue caused by increased cell division, often an initial stage in the development of cancer). These flies did not show an increased likelihood of being preyed upon by jumping spiders (Fig. 3a). However, jumping spiders were more successful at catching flies bearing an advanced stage of cancer (esg^{ts} > *UAS-Ras*^{v12}, *UAS-APC-IR*) compared with healthy flies (Fig. 3b). Furthermore, the preference index for sick individuals increased with the length of time after tumour induction (Fig. 3c; ordinal logistic regression: LRT = 8.07, $df = 1$, $P = 0.004$).

DISCUSSION

Many diseases do not kill their hosts and are considered benign in optimal conditions, such as in a clinic or laboratory. However, it is very likely that nonlethal illnesses still increase the risk of mortality through indirect interactions with other environmental factors. Indeed, being sick may reduce foraging and mating abilities and increase the risk of lethal superinfections or of being preyed upon. Even though many biological questions are presently being addressed using an integrative approach, the question of whether a nonlethal disease is truly benign in natural conditions seems to have been overlooked in many cases. We hope to generate interest in evaluating the lethality of diseases when their interaction with other risks, such as predation, is considered. Chronic infection by a wild-caught *Drosophila* pathogen did not significantly affect the risk of being preyed upon in the laboratory. In contrast, we observed that while the presence of early-stage tumours did not change predation risk, the presence of advanced cancer did, compared to age-matched controls.

Little is known about selective predation in individuals with noninfectious diseases. The prevailing opinion that general health, which can be affected by noninfectious sickness, correlates with the risk of being preyed upon, is largely observational (Genovart et al., 2010; Hoey & McCormick, 2004). Although we used different species of jumping spiders for the two assays, our results on selective predation suggest a stronger selective pressure arises from the progression of a noninfectious disease than from chronic infection by a natural bacterial pathogen, in this prey–predator pair.

Cancers are common in multicellular organisms and can occur whenever cells evade the normal cell checkpoints that control cell division, proliferation and apoptosis, leading to uncontrolled cell division (Aktipis et al., 2015). Individuals always have some tumours, most of which never become lethal (Abu-Helil & van der Weyden, 2019; Bissell & Hines, 2011). Our understanding of oncogenic phenomena in wild populations of animals is limited, in particular whether tumours that are clinically nonlethal affect the wellbeing of organisms in the wild (McAloose & Newton, 2009; Pesavento, Agnew, Keel, & Woolard, 2018; Vittecoq et al., 2013, 2015). Theoretical modelling further suggests that biotic interactions complicate the predictions regarding the impact of cancer on populations and that prey and predator populations are likely to suffer differently (Perret et al., 2020). If tumour formation is inevitable, it is likely that multicellular organisms have evolved ways to control and tolerate them, perhaps resulting in a trade-off between surviving the tumour and surviving other perils, such as infections or predation (Pavard & Metcalf, 2019). In some cases, selection for tumour tolerance may have arisen from selection for tolerance to other factors, perhaps explaining why early stages of cancer, such as the colon hyperplasia that we induced in *Drosophila*, do not change the likelihood of being preyed upon. In our study, when the tumour developed into a cancer, predation of the flies increased, suggesting that uncontrolled tumours strongly increase the likelihood of being preyed upon. This conclusion supports the

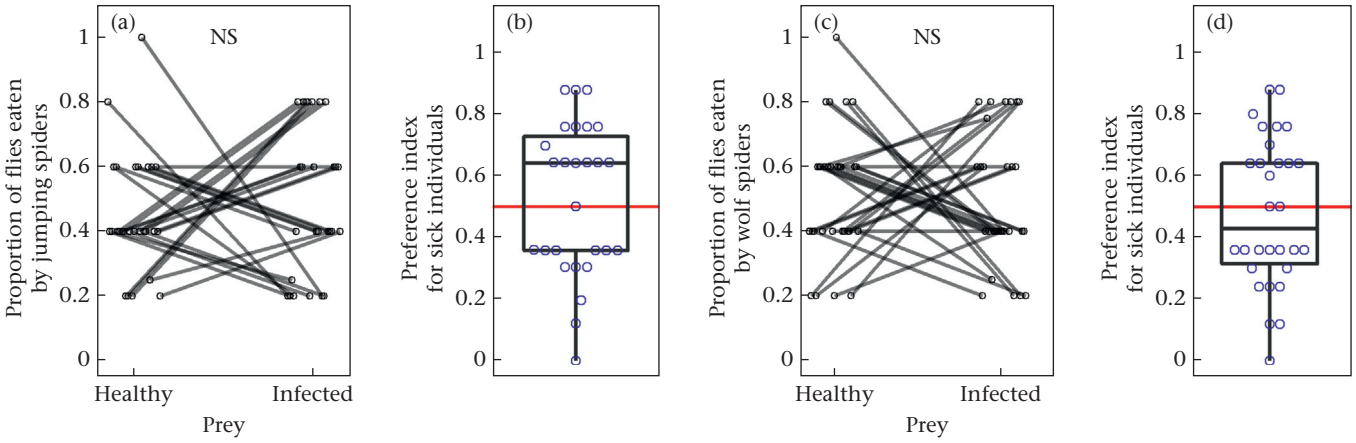

Figure 2. Predation by (a, b) jumping spiders and (c, d) wolf spiders on a population of *Drosophila melanogaster*. Flies were either healthy or chronically infected with *P. rettgeri*. Each dot in (a) and (c) represents the proportion of individuals eaten ($N = 5$ flies) and the lines connect the groups of individuals from the same trial. Each trial represents 10 flies (five from each type) presented to one spider at the same time. The preference index of spiders, represented by blue circles and of which 25th, 50th and 75th percentiles and range are described by box plots in (b) and (d), is calculated as in Manly (1972) and ranges from 0 (preference for healthy flies) to 1 (preference for sick flies). The red line corresponds to an index of 0.5 (i.e. no preference). (a) Hypergeometric test: $N = 27$ trials, $P > 0.05$, (b) median preference index = 0.64; (c) hypergeometric test: $N = 30$ trials, $P > 0.05$, (d) median preference index = 0.43.

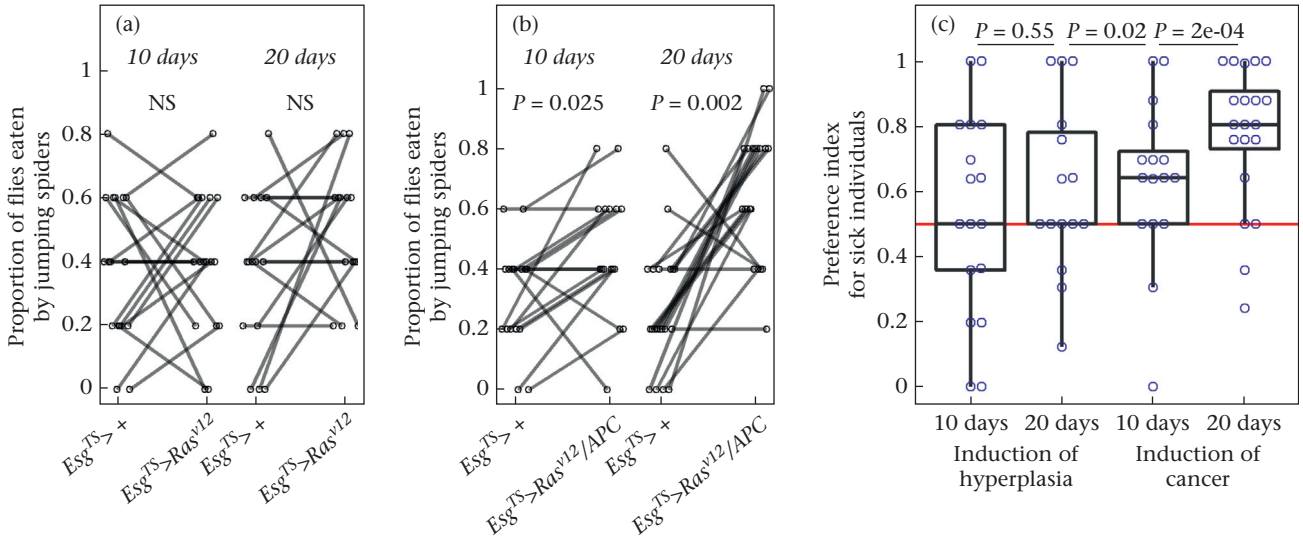

Figure 3. Predation by jumping spiders in a population of *Drosophila melanogaster* that were either healthy or sick with induced colon tumours (hyperplasia). Tumour size increased with induction time, during which uncontrolled cell division occurred. (a) Proportion of $esg^{TS} > Ras^{v12}$ flies eaten in which uncontrolled cell division was triggered for 10 days ($N = 17$ trials) or 20 days ($N = 15$ trials) to lead to hyperplasia. (b) Proportion of $esg^{TS} > Ras^{v12}$, *APC-RNAi* flies eaten in which fast uncontrolled cell division was triggered for 10 days ($N = 16$ trials) or 20 days ($N = 20$ trials) to lead to cancer. Each dot in (a) and (b) represents the proportion of individuals eaten ($N = 5$ flies) and the lines connect the groups of individuals from the same trial. Each trial represents 10 flies (five from each type) presented to one spider at the same time. (c) The preference index of spiders, represented by blue circles and of which 25th, 50th and 75th percentiles and range are described by the box plots, is calculated as in Manly (1972) and ranges from 0 (preference for healthy flies) to 1 (preference for sick flies). The red line corresponds to an index of 0.5 (i.e. no preference).

idea that individuals with uncontrolled tumours will suffer the risk of increased predation compared with healthy individuals. Predation is a critical force shaping natural selection (Wade & Kalisz, 1990). By removing prey genotypes susceptible to tumours, predators are likely to have selected for the tumour tolerance largely observed in nature (Bissell & Hines, 2011). Furthermore, by removing individuals with advanced tumours, predation may explain why cancerous animals are rarely recorded in necropsies of wild animal populations (Vittecoq et al., 2013).

We do not know why cancerous flies are more predated than their age-matched controls or even if this result could be to some extent dependent on the sex of the fly. Jumping spiders have been shown to be able to choose prey based on odour and coloration (Vickers & Taylor, 2018). It would be difficult to speculate why such behaviour would have evolved in the context of cancer, but we cannot exclude that the spiders recognized and preferred eating cancerous flies. In a recent study, assays of flies bearing intestinal cancers, notably in a different genetic background, showed that induction of intestinal cancer does not overtly affect fly locomotion (Dawson et al., 2018). However, there remains the likely possibility that cancerous flies have worse reflexes than healthy flies, and that subtle locomotion differences may be enough to explain a difference in the chance of escaping predation. Our results lay the premise for future studies on understanding the mechanisms explaining the reasons for this difference.

The progression of cancer can, in many ways, be compared with infectious disease. In fact, cancer cells have already been considered as a parasitic species consuming the host's resources after having emerged from healthy cells (Capp & Thomas, 2020; Duesberg,

Mandrioli, McCormack, & Nicholson, 2011). However, even if both reduce viability and survival, infectious diseases are, unlike oncogenic processes, under selective pressure to ensure transmission of the pathogen to another host. For noninfectious diseases such as cancer, selective predation could increase the selection against the sickness, as diseases that are moderate and nonlethal could lead to a higher risk of the host being preyed upon, resulting in mortality rates that are similar to those of infectious diseases. With infectious diseases, there may be additional consequences. First, selective predation could affect the transmission of pathogens, spreading them through predator faeces over long distances. Second, it might affect epidemics, either preventing them by removing parasite spreaders from the host population (Duffy et al., 2005) or increasing their likelihood of occurrence by dispersing parasites instead of containing them in dead hosts (Strauss et al., 2016). An additional consideration is that predation may affect the evolution of parasite virulence. It is generally assumed that predation can reduce virulence because hosts with rapidly proliferating parasites would suffer more from the infection and may be eaten before transmitting the parasite to another host, whereas the less rapidly proliferating parasite would have a lower impact on host health and would be transmitted before the host is eaten (Moller et al., 2010). Predation could also reduce virulence through reducing pathogenicity, that is by inducing less damage to the host. Therefore, either through reducing pathogenicity or proliferation, predation is expected to reduce disease-associated symptoms. The bacterium studied here, *P. rettgeri*, was obtained from the wild and is prevalent in populations of *D. melanogaster* (Juneja & Lazzaro, 2009). The infection did not increase predation by the two species of predator we used in our study, despite the fact that it was chronic and that the immune response was activated (Chambers et al., 2019; Duneau et al., 2017), This result supports the hypothesis that chronic infections are selected for, such that the symptoms that increase predation are reduced.

It is reasonable to assume that the success of predators is not simply due to favourable luck. In fact, selective predation may be more the rule than the exception and is likely to have a role in the evolution of diseases, infectious or not (Møller, 2008). On the one hand, selective predation on sick individuals is likely to select against parasites or genetic diseases more strongly than if selection occurred upon disease-mediated host death later in life in the absence of predation. On the other hand, in the same way that some parasites evolved to manipulate their host to increase transmission to intermediate hosts (Hughes & Libersat, 2019), parasites may have evolved to make their hosts less conspicuous to predators, for example by interfering with the search for mates or by lessening the effects of the disease on the host, that is, by reducing symptoms. Because cancer progression generally results in the death of the organism, we cannot expect the incidence of lethal cancer to have evolved in the same way as parasites, except for transmissible cancers such as in Tasmanian devils (Dujon, Bramwell, Roche, Thomas, & Ujvari, 2021). We argue that selective predation on prey with cancer may be one of the reasons why tumours are commonly tolerated in animals, where advanced cancer is only rarely detected.

Author Contributions

D.D. and N.B. designed and performed the study. D.D. analysed the data. D.D. wrote the manuscript with the contribution of N.B.

Data Availability

All data are publicly available at https://github.com/dduneau/Dataset/tree/main/Data_Duneau_AnBeh_2022.

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