Review: Colorectal cancer in humans and non-human mammals

Mandy E. Kauffman, Graduate Student, PATB5515, Department of Veterinary Science,
University of Wyoming, Laramie, WY, USA

ABSTRACT

Colorectal cancer (CRC) is the third most common cancer occurring in humans in the United States, killing approximately 50,000 people annually. Two routes of CRC development are well-described in humans; both involve a series of multiple mutations and a step-wise transition from normal cells to metastatic cancer. CRC occurs in domestic dogs, cats, and captive primates, but is rarely observed in wildlife species.

INTRODUCTION

According to the American Cancer Society, colorectal cancer (CRC) is the third most common cancer both diagnosed in and killing both sexes in the United States. In the United States, 1 in 20 individuals will develop CRC in their lifetime. Almost 50,000 people are expected to die from CRC in the United States in 2011 (1).

Known risk factors for CRC include exogenous characteristics, such as diet high in red/processed meats, physical inactivity, obesity, smoking, alcohol use and type 2 diabetes. Endogenous factors include age, history of colorectal illness (previous polyps/cancer, inflammatory bowel diseases), family history of CRC, inherited genetic defects, and racial/ethnic background (2).

There are two general types of CRC characterized in humans: sporadic and inflammatory bowel disease (IBD) associated (IBD-associated) (16). Both types of CRC require multiple
mutations, follow a progression from dysplastic cells to malignant cancer, and exhibit imbalances of substances (e.g. cytokines, proteins). Prognosis for both types is similar (survival around 50% after 5 years), although the age of onset is typically earlier in the IBD-associated form (16). In most cases of sporadic CRC, the initial lesion is a benign polyp that then matures into a highly dysplastic adenoma. This adenoma then progresses to an invasive cancer that can eventually metastasize (13). In IBD-associated CRC, malignant cells originate directly from the intestinal mucosa without the formation of a polyp (16). Early stages of CRC are not typically painful, but victims may experience symptoms such as unexplained weight loss, fatigue, nausea and vomiting, gassiness/full feeling, and bowel disturbances (e.g. diarrhea/constipation, blood in stool, changes in size or frequency of bowel movements). Several screening tests are available to identify and remove polyps before they can become cancerous (15). Prophylactic measures, such as frequent/early screening or removal of portions of intestine, are utilized in individuals with severe defects associated with rapid growth or very high risk of developing CRC (13).

Life expectancy following diagnosis depends on the stage of disease, and can range from 74% (if diagnosed at stage I) to 6% (if diagnosed at stage 4) (3).

GENETIC FACTORS IN HUMANS

Hereditary CRC

Some rare forms of CRC develop as a result of inherited defects. These inherited syndromes account for a very low proportion of CRC cases (≤5%), but have severe effects. As such, drastic prophylactic measures are often taken when individuals have these defects (13). Due to their rarity, the genetic mutations observed in these cancers are described below, but are not considered in the remainder of this review.
An inherited defect in mismatch repair genes is seen in an autosomal dominant disease known as hereditary nonpolyposis colon cancer (HNPCC, or Lynch Syndrome), where defects in genes MLH1 and MSH2 result in a high lifetime risk of cancer (80%) with early onset (age 45 or less). Individuals carrying this defect can develop cancer very rapidly, and as a result, more frequent screening is recommended (13).

If MYH, a base excision repair gene, is inactivated due to inheritance of two inactive alleles, oxidatively damaged guanine residues cannot be excised. Individuals who inherit two inactive alleles have almost 100% chance of developing colon cancer by age 60, and prophylactic removal of the colon is often electively done (13).

**Sporadic and UC-Associated CRC**

As described briefly above, two routes of CRC development in humans are recognized (Figure 1).

![Figure 1](image)

**Figure 1.** Proposed route of CRC development in humans (adapted from 13, 16). 1s: APC, DNA hypomethylation; 2s: K-ras; 3s: c-src, microsatellite instability; 4s: p53, microsatellite instability. 1uc: aneuploidy, sialosyl-Tn; 2uc: p53, microsatellite instability; 3uc: p53, K-ras, c-src, microsatellite instability; 4uc: APC, Rb, other TSG.

In humans, several genomic instabilities have been implicated in the development of CRC. In both types of CRC, a series of mutations must occur in order for cancer to occur, which is consistent with the “multiple hit” theory of cancer development. The exact order and type of changes differs among types of CRC (Figure 1) (16).

**Sporadic CRC**
The first alteration in the genome observed in the development of spontaneous CRC is a mutation inactivating the gene encoding a protein called adenomatous polyposis coli (APC). APC forms part of a complex that degrades an oncoprotein called β-catenin before it can move from the cytoplasm to the nucleus through the Wnt signal transduction pathway. β-catenin forms part of a transcription factor involved in cell activation (13). APC has been described as the “gate-keeper” of this pathway; aberrant activation of this pathway can imbue an advantage in growth (19) (Figure 1). This mutation is not observed often in IBD-associated cancer, and may explain the lack of polyp formation in this type of cancer (15).

Additionally, in early stages of transition between normal colonic epithelium and adenomatous growth, changes in methylation of DNA may be observed. In normal cells, ordered methylation serves to stabilize DNA (Figure 1). In neoplastic cell genomes, general hypomethylation of the DNA may be observed, with focal areas of hypermethylation (11). Excessive and aberrant methylation of promoter regions (cysteine-guanine repeats, or CpG islands) can result in silencing of genes that express products such as MLH1 (a DNA mismatch repair protein) and cause other regions of DNA to be more prone to mutation (13).

Marking the transition between an early adenoma and an intermediate adenoma (Figure 1, 2s) is aberrant activation of an oncogene called KRAS, which can promote the growth of numerous, hyperplastic polyps (13).

A chromosomal mutation that results in increased expression of c-src (Figure 1) marks the transition from intermediate to late adenoma (16; 8). C-src is suspected to aid in metastatic capability via many mechanisms. One proposed mechanism is increased expression of enzymes involved in processing of metals, which play a role in invasion of lymphatic and vascular
systems (8). Increased proliferative ability through c-src overexpression allows for enhanced growth of adenomas (8).

Chromosomal instability, characterized by loss of heterozygosity at several loci, is observed in up to 85% of CRCs and results in impaired or lost function of tumor suppressor genes (13). The tumor suppressor protein p53 is most commonly affected. p53, which plays a role in cell-cycle arrest and apoptosis, can be inactivated by mutations in its coding gene, TP53. Both alleles of TP53 must be affected to induce this change; this often occurs through the effect of a chromosomal abnormality at one allele, and a chance mutation in the other allele (19). Finally, missense mutations (e.g. frameshifts) can completely inactivate TGF-β, which results in inactivation of SMAD4. SMAD4 seems to function in tumor suppression (5). This type of mutation appears to play a role in the advancement of adenomas to dysplastic or malignant neoplasias (13).

UC-Associated CRC

Many of the same pathways leading to sporadic CRC occur in the development of UC-associated CRC, albeit in different stages of cancer development. Only the mutations occurring in UC-associated CRC not described for sporadic CRC above are elaborated upon here.

In the case of UC-associated CRC, chronic inflammation of the intestinal epithelia is the basis for tumor development by two routes. Firstly, ongoing repair processes in areas of inflamed epithelia result in increased cell turnover, with more chances for mutations to occur. Secondly, the response of neutrophils and macrophages to chronically inflamed sites results in the production of free radical species that can directly damage DNA. Both of these mechanisms can lead to aneuploidy (abnormal chromosome numbers) (17). In addition to chromosomal
changes, expression of an antigen known as sialosyl-Tn has been associated with pre-dysplastic changes in UC-associated CRC (9) and could serve as a marker for pre-cancerous changes.

Mutations in p53 (Figure 1), as described above for sporadic CRC, can render affected cells unable to appropriately respond to severe DNA damage. This is particularly concerning in the case of UC-associated CRC, where chronic inflammation of the intestinal epithelia is likely to generate extensive aneuploidy (17). In fact, this change is seen in many epithelial cells lining a colitic colon, even in the absence of observable dysplastic changes (17). Histological studies have demonstrated that chromosomal abnormalities increase in number and severity as cells morph from normal to cancerous (Figure 1), and that cells in mucosa adjacent to UC-associated CRC demonstrate significant chromosomal abnormalities (17). Due to the loss of p53 function, these cells, while not yet cancerous, will be unable to remove themselves from the population via apoptosis and may therefore be at risk of contributing to cancer in the future (17).

Microsatellite instability is observed in UC-associated CRC; telomeres become progressively shortened as cells transition from normal to cancerous. Decreased telomere length causes genomic instability, and likely makes it easier for additional genetic mutations to develop (17).

Finally, mutations in APC (as described above) or tumor suppressor genes (Figure 1) such as retinoblastoma protein (Rb) are observed in CRC cells. Aberrant expression of Rb can result in uncontrolled cell growth and inhibition of apoptosis (8), allowing cells with severe genetic damage to continue through the cell cycle and progress to sustain further genetic damage.

It is important to note that, like in sporadic CRC, UC-associated CRC also involves a step-wise progression from normal to cancerous cells, and this process occurs via an increasing burden of mutations that allow changes in cell behavior. A considerable number of genes have
been identified that likely play a role in the colon cancer phenotype, and the phenotype of any
given colon cancer is greatly variable. This plethora of differences makes it difficult to identify
the biological outcome of individual mutations, since many mutations may result in the same
observable effects (13) and respond differently to specific treatments.

CRC IN NON-HUMAN MAMMALS

Domestic animals

Among the companion animals, dogs are most commonly affected (17). In dogs, although neoplasia typically arises directly from the intestinal epithelia, polyps can also form and progress to cancer. Colon adenocarcinoma in dogs does not frequently metastasize (7). Cats are less commonly affected, but in this species an exceptionally high rate of metastasis is observed (6). Sheep and oxen can also be affected (9; 17). Some genetically engineered or chemically induced rodents (mainly mice) serve as models for IBD and CRC (16), but these diseases are not described in wild rodents. It is clear that we are more likely to observe neoplastic disease in companion animals as opposed to livestock due to the companion animal's relatively long lifespan and close contact with humans.

Captive wildlife

Nonhuman primates in captivity are similar to humans in that they experience a greater occurrence of neoplastic diseases as they age, with intestinal cancer being the most common (18). Cotton top tamarins (*Saguinus oedipus*, CTT), a species often used in biomedical laboratories and zoos, commonly suffer from a form of colitis known as "marmoset wasting syndrome". This disease often progresses to colonic adenocarcinoma without the formation of polyps. The relatively high incidence of colitis progressing to colonic adenocarcinoma is observed exclusively in domestic colonies of CTT, and is not described in wild specimens (12).
The clinical pathology and progression of colonic cancer that CTT experience most resemble the IBD-associated form of colon cancer seen in humans (4), although evidence for molecular pathways similar to that observed in humans for this disease process was not uncovered in the course of this research.

**Wildlife**

In wild animals, cancer is not typically a leading cause of death. This is because (1) wild animals often do not live long enough to accumulate a sufficient number of mutations to develop cancer, and (2) wild animals suffering from disease are likely to die of other causes (e.g. predation, starvation) before succumbing to disease (14). A study of beluga whales (*Delphinapterus leucas*) in the St. Lawrence Estuary (SLE) of Quebec, Canada in the 1990s indicated a high incidence of gastrointestinal cancers (14). These cancers are rarely observed in other cetacean species, or in beluga whales living in other Arctic regions. The rate of cancer observed in this population of beluga whales was similar to that observed in humans (14). Belugas have a relatively long lifespan (≥50 years), sufficient to accumulate a number of genetic changes. Additionally, belugas in the SLE feed on benthic invertebrates that are contaminated with higher-than-elsewhere concentrations of polycyclic aromatic hydrocarbons (PAHs). It is suspected that processing of PAHs within the beluga's digestive tract generates carcinogenic compounds. Finally, because this population of whales is relatively isolated, a founder effect (inbreeding) may be compounding mutations (14). High rates of cancer have been observed in other highly inbred species such as black-footed ferrets (*Mustela nigripes*) (14).
DISCUSSION/CONCLUSIONS

A number of genetic mutations have been described in the progression of intestinal epithelia from normal to CRC in humans. Development of sporadic and UC-associated colon cancers in humans requires multiple sustained mutations. The recognized mutations generally imbue cells with the capabilities to bypass normal regulation and continue to proliferate in the presence of dangerous DNA mutations. Many of the mutations eventually leading to cancer are the same through both mechanisms, although the underlying theme in development of UC-associated cancer is chronic inflammation and increased cell turnover.

Colonic adenocarcinoma is also described in domestic animals, particularly dogs and cats. These animals generally have a long lifespan compared to their wild counterparts, and disease is likely to be identified when owners observe abnormal behaviors and take the animal to the veterinarian. Evidence for the roles of diet and obesity in human CRC development has been compiled, and it seems possible that these could be factors for domestic animals as well. However, these topics are beyond the scope of this review.

In wildlife, the role of cancer is less clear. Most wild animals will die of predation, starvation, or traumatic injury before reaching an age at which many mutations could accumulate. If the current theory of cancer development (that a series of mutations are necessary) is true, it is unlikely that many wild animals suffer from cancer. If wild animals do suffer from forms of gastrointestinal cancer, they are likely to die from other causes (e.g. predation) due to decreased fitness long before lesions are grossly apparent. However, it does seem intuitive that longer-lived mammals could develop cancer late in life, particularly when exposed to carcinogens or other risk factors. The role of diet may come into play here as well;
however, environmental contamination also warrants consideration. These topics are again beyond the scope of this review.

While it is helpful to understand the specific mutations that lead to development of CRC, knowledge of how environmental or dietary factors contribute to cancerous changes would be incredibly useful. The asymptomatic and/or nonspecific early stages of CRC, coupled with the unpleasant nature of screening tests in humans, make early detection of disease problematic. The role of diet is particularly intriguing; it is generally accepted that a diet high in red/processed meats contributes to an increased risk of developing colon cancer, while fruits/vegetables and high fiber diets have been suggested to prevent CRC development. However, surprisingly few studies have been conducted to uncover why this might be the case. Improved understanding of the role diet and environment play at the molecular level of CRC development could potentially lead to great strides in prevention of this disease.
Literature Cited


