Activity 1: No Cut-and-Dried Answers

Based on video and online text content

15 minutes (10 minutes before and 5 minutes after the video)

Setup

Before viewing the video on Cell Biology and Cancer, look at the ten statements on the Yes/No, But… handout. Take a few minutes to read each, and write "Yes" if you think the statement is true or "No" if you think it is false. The statements are rather cut-and-dried, but biology—especially cancer biology—rarely is. Therefore, for some of the statements you might want to answer "Yes, but…" or "No, but…" In those cases, write a phrase or two about what makes you want to qualify your answer. After viewing the video and reading the text, look through your list again to see if any of your ideas about cancer were changed and if any were reinforced.

Materials

- One copy of the Yes/No, But… statements per person (master copy provided)
- Tips and Suggested Answers

Yes/No, But...

Write either "yes" or "no" next to each question. You may want to qualify your answer with a phrase or two about why this cut-and-dried statement really can't be answered with a simple yes or no. See the Tips and Suggested Answers for possible points of view.

1. Cancer "runs in families"; it is inherited from one's parents.

2. Cancer is a genetic disease.

3. "Cancer" is really hundreds of different diseases.

4. Over half of cancers in this country are preventable.

5. Scientists no longer believe that viruses cause cancer.

6. Oncogenes are cancer-causing genes.

7. The function of "tumor suppressor genes" is to suppress tumors.

8. Telomeres (the ends of eukaryotic chromosomes), get shorter each time the chromosome is replicated and the cell divides.

9. Prostate cancer can be diagnosed with a simple blood test for prostate-specific antigen (PSA).

10. Twenty-five percent of people in the U.S. will develop cancer in their lifetime.

No Cut-and-Dried Answers: Possible Answers and Qualifying Statements

1. Cancer "runs in families"; it is inherited from one's parents.
   A person can inherit a *predisposition* or an *increased risk* for certain types of cancer by inheriting "mutant" alleles of genes that are involved in cell division.

2. Cancer is a genetic disease.
   Cancers result from mutations in genes, so they are genetic diseases. However, environmental factors like exposure to mutagens and carcinogens may cause the mutations that lead to cancer.

3. "Cancer" is really hundreds of different diseases.
   All cancers, fundamentally, are cells undergoing uncontrolled cell division. However, there are many mutations and combinations of mutations that can lead to this outcome.

4. Over half of cancers in this country are preventable.
   Preventing most of the cancers in the U.S. would require stopping smoking, cleaning up environmental hazards, and changing our diet—an ideal goal that might not be entirely practical. Also, spontaneous mutations caused by errors in DNA replication and other random events mean that some cancers are inevitable.

5. Scientists no longer believe that viruses cause cancer.
   Viruses are no longer thought to be the sole cause of cancer, but some viral infections are associated with cancers—for example Hepatitis B and liver cancer, or papilloma virus and cervical cancer—because they can cause mutations that contribute to cancer.

6. Oncogenes are cancer-causing genes.
   An oncogene is a mutated form of a gene that normally functions in growth and development; the mutated gene can contribute to the development of a cancer cell. The unmutated version is called c-oncogene, cellular oncogene, or proto-oncogene, although the term "oncogene" is sometimes used for both the mutated and unmutated form.

7. The function of "tumor suppressor genes" is to suppress tumors.
   Tumor suppressor genes did not evolve to suppress cancers, but to play a part in the normal regulation of cell division. However, when their normal function is lost through mutation, this contributes to cancer.

8. Telomeres (the ends of eukaryotic chromosomes), get shorter each time the chromosome is replicated and the cell divides.
   Telomeres get shorter with each cell division in normal adult human cells. This is not true in all cells; for example, in germ line cells, many plant cells, and some cancer cells, the telomeres do not get shorter.

9. Prostate cancer can be diagnosed with a simple blood test for prostate-specific antigen (PSA).
   PSA is normally present in the blood of adult males, so just its presence, even at a somewhat high level, does not definitively indicate prostate cancer. Not all prostate cancers cause elevated levels of PSA. However, a high level of PSA is an indication that further testing should be done.

10. Twenty-five percent of people in the U.S. will develop cancer in their lifetime.
    The lifetime risk for women in the U.S. is 1 in 3; for men it is 1 in 2. However, these are generalized numbers for the entire population.

Activity 2: The Price of Proto-Oncogenes

Based on video content

15 minutes (during the video)

Setup

Stop the video after about five minutes, just after Dr. Robert Weinberg says, "Without the proto-oncogenes, embryos wouldn't be able to develop, adult tissues would not be able to be maintained. However, the price of carrying these proto-oncogenes in our genomes is occasionally they become damaged and mutated and convert into oncogenes and thus become converted into agents for causing cancer."

Take a few minutes to think of what cellular functions normal proto-oncogenes might have. Remember, these are genes that have a role in normal cell division for growth, development, and cell replacement. Make a list of some functions they might perform, then discuss the discussion questions. Restart the video and see how some proto-oncogenes normally function.

Materials

- One transparency of the Discussion Questions

Discussion Questions

1. One of the proto-oncogenes that is frequently found to be mutated in a cancer encodes the protein Ras. It is found just on the inside of the cell's plasma membrane and is activated when signaling molecules, like growth factors, bind receptors. What might Ras be doing?

2. Some studies have found an association between long-term hormone replacement therapy for menopause symptoms and an increased risk for certain types of cancer. What might be the connection between hormone therapy and an increased risk of cancer?

3. One treatment for some types of cancer includes drugs that block estrogen receptors and antiandrogens, which block testosterone production. Speculate on how this therapy might slow or prevent the growth of cancerous cells.

Activity 3: Family History

Based on video and online text content

60 minutes

Setup

In 1990, the first gene associated with early-onset inherited breast cancer was mapped to chromosome 17. The technique for mapping a gene to a chromosome is to follow simultaneously the inheritance of the trait caused by the gene, and the inheritance of easily followed sequences called markers on all the chromosomes. Genes and markers that are on different chromosomes or far apart on the same chromosome will segregate randomly. Genes and markers that are close to each other on a chromosome tend to be inherited together. Only occasionally will crossing-over occur between them. Because the chromosomal location of the marker is known, the tendency of a trait and a marker to inherit together maps the approximate location of the gene on a particular chromosome. The frequency of the occasional crossing-over events give the distance between the marker and the gene.

The technique is a great deal of work, but it is a classic pedigree and statistical analysis. In this exercise, you'll see some of the pedigrees used to locate the BRCA1 gene and you will go over some of the theory behind the technique. Working in pairs, start by discussing the background questions. Then get copies of the Pedigrees and Data sheet and LOD Score Information sheet, and work through the exercises. As a group, talk about the discussion questions at the end.

Materials

- One copy of the Background Questions for each person (master copy provided)
- One copy of the Pedigrees and Data sheet for each person (master copy provided)
- One copy of the LOD Score Information for each person (master copy provided)
- One copy of the Discussion Questions per person (master copy provided)
- Tips and Suggested Answers

Background Questions

Read these questions and discuss them before starting on the Pedigrees and Data sheet. Answers are in the Tips and Suggested Answers.

1. Breast cancer can arise from both inherited and spontaneous mutations. The alleles that are responsible for inherited breast cancer are incompletely penetrant, which means that people who inherit the allele do not always show the phenotype. How does this cause problems for studying inherited cases of breast cancer? What criteria would you use to find families to use in a study of inherited breast cancers?

2. How would you confirm cases of breast cancer, even if the person in the family was deceased? How would you confirm that someone did NOT have breast cancer?

3. What would you use for chromosome markers to follow along with the inherited trait?

4. Up to 25 percent of pedigrees are incorrect because parentage is not as expected. What would you do to correct for this?

Pedigrees and Data

After reading and discussing the background questions, work through these pedigrees by answering the following questions. The pedigrees are modified from ones done for the study that identified the chromosomal region with BRCA1.

1. Do the pedigrees suggest autosomal or sex-linked inheritance? Dominant or recessive?

2. Read the LOD Score Information sheet. If a hypothesis about linkage between a gene and a marker has a high LOD score (for example, 4) what does it mean? If a hypothesis for linkage has a low LOD score (for example, -2) what does it mean?

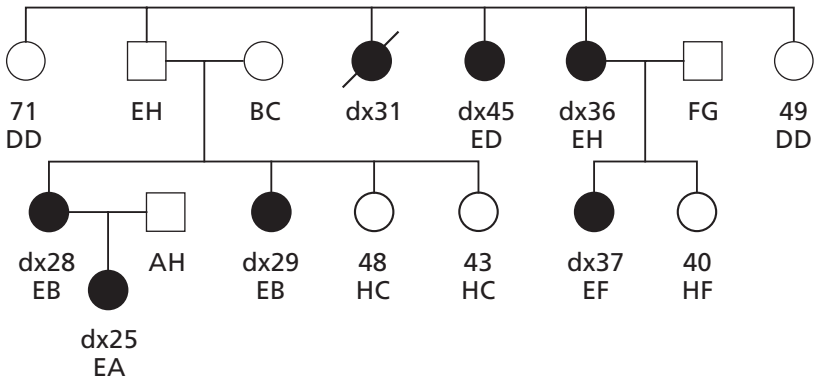
3. For each family, look at the pedigree and the LOD scores and answer these questions: Is there evidence of linkage between marker D17S74 and breast cancer? If not, give an explanation in a few sentences to your partner and see if s/he agrees, disagrees, or has any clarifications to add. If there is evidence of linkage, what allele of the marker, in this family, is linked to the disease allele of the gene? Why is it not the same in all families?

Legend for Pedigrees

Circle, Female	If living and unaffected–age at last interview for study is given.
Square, Male	If affected–age at diagnosis with breast cancer is given.
Open, Unaffected	If deceased–age at death is given.
Filled In, Affected	Two letters–represent allele of the DS17S74 marker, which was found to be the most closely linked to the breast cancer susceptibility gene.
Deceased	One letter–given when one allele is known, and the other is unknown.

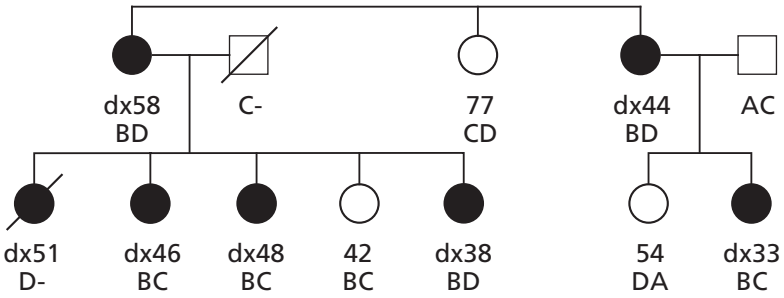
Family 1

mean age of onset: 33
LOD score for linkage of breast cancer to D17S74 (recombination fraction 0.001) = +2.36



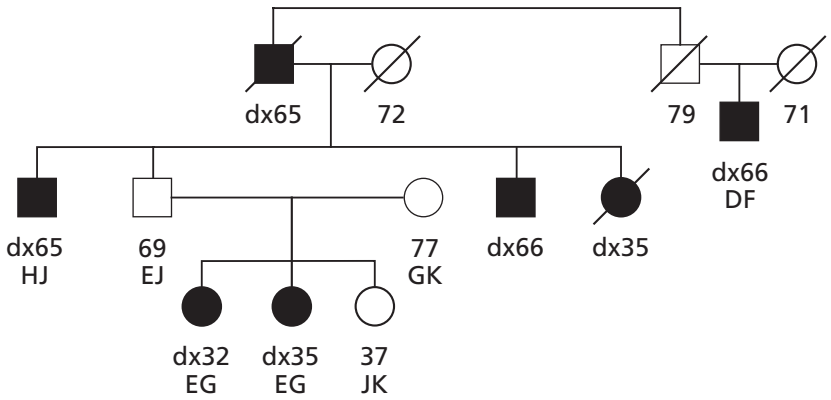
Family 7

mean age of onset: 44
LOD score for linkage of breast cancer to D17S74 (recombination fraction 0.001) = +0.7



Family 16

mean age of onset: 52
LOD score for linkage of breast cancer to D17S74 (recombination fraction 0.001) = -2.71



Sources: Hall et al. 1990. *Science* 250:1684

LOD Score Information

LOD stands for "log of the odds of linkage."

In this case, "linkage" means the gene for the trait of inherited tendency for breast cancer is located close on the same chromosome to a genetic marker—for example, a small, variable sequence that is easily followed. Traditionally, linkage is measured in units of recombination frequency, with one map unit equaling one percent recombination. In this case, we're following inheritance of risk for breast cancer and inheritance of a marker—for example a restriction fragment polymorphism or a single nucleotide polymorphism (SNP) (see the Genomics unit). If 1 individual out of a 100 observed showed evidence that crossing over changed the combination of marker and breast cancer gene on a chromosome, that would be a one percent recombination frequency, or one map unit.

To standardize the evaluation of evidence for linkage, the LOD is calculated. "Log of the odds" is the $\log_{10}$ of a ratio, calculated for a number of different possible values of X, as shown below:

$$\text{LOD} = \log_{10} \frac{\text{probability that the observed pattern of inheritance occurred by chance}}{\text{probability that it occurred because the gene and the marker are linked X map units apart}}$$

A series of LOD scores shows the probability of linkage at several certain distances. Because it is a $\log_{10}$ value, a LOD score of 3 means odds are 1000 to 1 in favor of linkage. LOD 4 means the odds are 10,000 to 1 in favor of linkage. LOD scores of 3 to 4 are generally accepted as indicating linkage.

Discussion Questions

Possible answers are in the Tips and Suggested Answers.

1. What are some explanations for pedigrees included in this study that showed negative LOD scores?

2. In the region identified by the linkage analysis were several candidate genes. Among them were a gene with homology to human epidermal growth factor receptor, a gene involved in steroid hormone synthesis, and a protein that binds the possibly anticarcinogenic retinoic acid. How would mutations in these genes contribute to cancer?

3. From the marker allele inherited, some of the women in the study should have inherited a breast cancer susceptibility allele, yet did not have breast cancer. What are some explanations?

4. Breast cancer is not the most common cancer in women (lung cancer is the most common). Only 5–10 percent of breast cancers are inherited, and of these, only 15–20 percent are attributed to mutations in BRCA1 or BRCA2. Do you think it is worth the effort to find genes implicated in inherited breast cancer, or is it better to spend the research dollars to investigate the 90–95 percent of breast cancers that are not inherited?

Family History

Background Question Answers

1. The criteria used by the authors of this study were families with extended history and many cases of breast cancer, younger age at diagnosis, frequent bilateral breast cancer (both breasts), and higher incidence of breast cancer in men in the family.
2. The authors of this study obtained pathology records, medical records, or death certificates for any individuals who had had surgery. For individuals who did not have breast cancer, the authors relied on self-reporting for living family members, and death certificates or reports from relatives for deceased family members.
3. The authors of this study used VNTRs (variable number tandem repeats), which are repeated sequences whose number varies widely in the population; and RFLPs (restriction fragment length polymorphisms), which are sequence variations that can be detected with a restriction enzyme.
4. The authors of this study followed inheritance of 183 different markers to confirm parentage.

Discussion Questions, Possible Answers

1. Explanation of LOD scores

   Note that for families 7 and 16, with low and negative LOD scores, the age of onset is relatively late. The gene identified in this study is responsible for early-onset familial breast cancer. The explanations given by the researchers for low and negative LOD scores in some families include a mutation in a different gene (for example, the BRCA2 gene that was discovered later); or a high incidence of spontaneous cases of breast cancer just by chance.

2. How might mutations contribute to cancer?

   Actually, BRCA1 turned out to be a completely new gene. None of the candidates first identified in the region were responsible for inherited breast cancer.

3. Explanations between inheritance of marker but not breast cancer

   Linkage between particular markers and gene alleles can change if crossing-over occurs between them. Inheritance of the breast cancer alleles just increases risk, it does not always result in cancer.

Activity 4: Dilemmas of Cell Biology

Based on video and online text content

60 minutes

Setup

The topic of cancer is woven tightly into other topics of biology—like cell division, cell death, aging, and medical ethics. This exercise comes with three packets of information, each addressing a different issue in which cancer research has an impact on another area of biology. Divide into three teams. Each team should take one packet of information, go through the exercises, and discuss the questions. After 15–20 minutes, pass your packet to the next team and take one from another team. Continue until all teams have gone through all packets.

Materials

- One copy of each of the three different Topic Packets (master copies provided)
- Three copies of the Cell Biology and Cancer unit online text chapter (available online at http://www.learner.org/channel/courses/biology)

Topic Packet 1: p53

Part1: As a team, discuss these points.

1. What is the function of p53?
   (Here's a suggestion for how to approach this part: As a team, make a list of what you know about p53, with one person writing down all the ideas. After a minute or so, organize your list into a description of p53's function.)

2. If you didn't cover this idea in question 1, consider how a loss-of-function mutation in p53 would affect cell division. Would this mutation be dominant or recessive? That is, would a mutation in one copy of the p53 gene be sufficient to see the phenotype or would two mutant p53 alleles be necessary?

3. Is p53 classified as a tumor suppressor or an oncogene?

4. The human p53 gene has been cloned and could, theoretically, be used in gene therapy. Come up with a strategy for introducing unmutated alleles of p53 into cells that have p53 mutations. What might be some of the dangers, drawbacks, or limitations of your strategy? What might be some of the advantages of your strategy over other cancer therapy methods?

   If your team is unfamiliar with gene therapy, read the following hints:

   a. Most current gene therapy techniques introduce a gene in an inactivated virus that can infect a cell but cannot produce more viruses.
   b. Some gene therapies are designed to integrate the introduced gene permanently into the chromosome, but the gene inserts into a random location. We cannot direct where in the genome the gene will be inserted, so it may disrupt or alter the expression of another gene.
   c. The introduced gene is not always expressed at precisely the same level as the normal gene. The cell with the introduced gene might express a little more or a little less of the protein than normal.
   d. Successful use of this gene therapy technique requires a virus that can be engineered to infect and not replicate. The virus must be able to access and infect the targeted cells. In addition, if the therapy is done by removing cells and infecting them in vitro, the corrected cells must be reintroduced into the patient.
   e. New gene therapy techniques may use small interfering RNAs (siRNAs) that *prevent* expression of a gene by causing its mRNA to be degraded.

5. Do you think there would be any consequences to introducing *too much* p53? If so, what would they be?

Part 2: After discussing points 1–5, read the following summary of work done by Dr. Lawrence A. Donehower of Baylor University and answer the following questions as a team.

In 1992, researchers in the Donehower lab made "p53 knockout" mice that had their p53 genes knocked out, so they completely lacked functional p53 protein. The mice died of cancer at an early age.

In 2002, they tried to make more mutant p53 mice, but these were not knockout mice. Instead, a p53 gene was introduced that still produced protein, but had a small change in the amino acid sequence. The mice they generated did not get cancer, but developed a different phenotype. They looked "old." They also had osteoporosis, shriveled organs, and a shorter lifespan.

6. What do you think happened? Explain the relationship between mutant p53 and the phenotypes it caused.

After discussing point 6, read the following.

Dr. Donehower's lab investigated the mice that became "old" quickly and, as you might have deduced, they were producing *extra* amounts of normal p53.

One of p53's functions is inducing apoptosis (programmed cell death). In a young organism, organs that require a continuous supply of new cells, like skin, blood, and intestinal lining, produce many new cells. In fact, they can produce more than are needed, by division of stem cells.

7. Why might extra p53 cause a young mouse to age prematurely?

8. UV light causes DNA damage that activates p53. What is a possible connection between UV light and skin that looks "old"?

9. People with Li-Fraumeni syndrome have mutations in the p53 gene that increase their risk of cancer by approximately 100-fold. At this point in our knowledge of p53 and our abilities in gene therapy, would it be possible, practical, and ethical to use gene therapy to correct Li-Fraumeni syndrome? If you would use gene therapy, would you use the technique that introduces an unmutated version of the gene, or a technique like siRNA that prevents expression of a gene?

Sources: *New York Times*. 2002. Cancer fighter exacts a price: cellular aging. Jan 8.;
Science. 2003. Aging and genome maintenance: lessons from the mouse? 299[5611]:1333–34. February 28.;
http://www.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?151623

Topic Packet 2: Telomerase

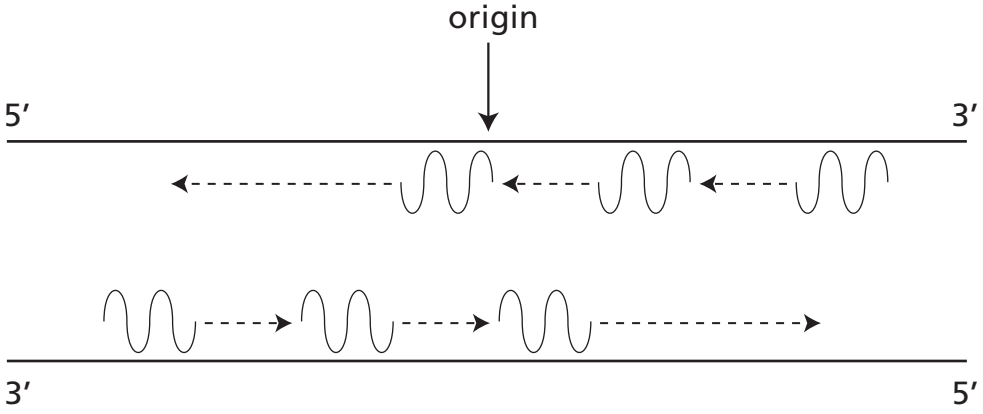
As a team, discuss these points.

1. Start by describing the telomeres of chromosomes and their functions as completely as possible. Review the video and Cell Biology and Cancer online text chapter if necessary. What happens to a chromosome end that lacks telomeric sequences? What are the consequences for the cell?

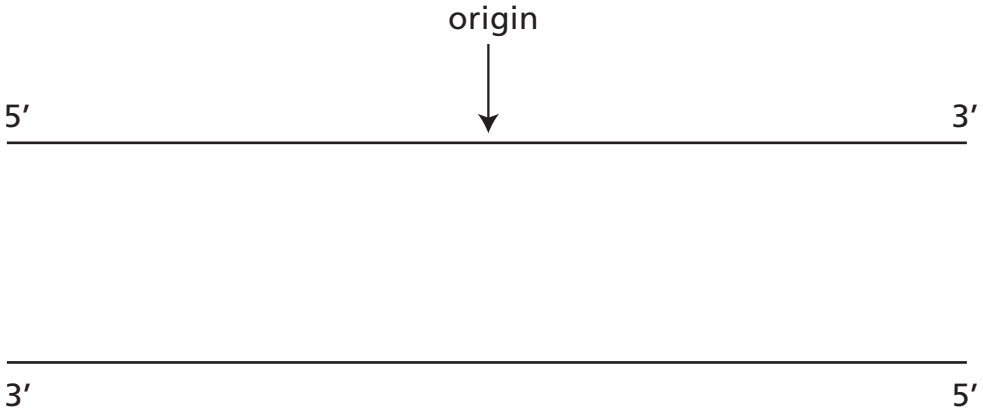
2. Complete this drawing of the replication of a linear chromosome by:
    a. Marking 5′ and 3′ ends on Part 1, and then filling in rest of the newly replicated strands and Okazaki fragments.
    b. Showing how the DNA will look as the RNA primers are removed on Part 2.
    c. Showing what the DNA polymerase that removes and replaces the RNA primers will use as a primer and what it will use as a template on Part 2.

Figure legend: Primers made by RNA primase are shown as wavy lines. The newly made strands are dotted lines. Their synthesis started from replication origins in the middle where the "origin" arrow indicates.

Part 1:



Part 2:



3. Using the drawing in 2b as a guide, describe the chromosomal replication problem that is solved by the enzyme telomerase. (Side issue: Do bacterial cells need telomerase? What about viruses?)

4. At which chromosome ends would telomerase be found?

5. In what types of human cells is telomerase active? (You can review Dr. Elizabeth Blackburn's interview in the video, or information in the online text.)

6. For a long time, it was thought that all DNA polymerizing enzymes required a template—a single strand with a sequence complementary to the strand the DNA polymerase enzyme would make. Look at the drawing above. How does telomerase work without a template strand?

   If your group is unfamiliar with the details of telomerase, read the following hint:

   Telomerase is not a single protein enzyme, but a complex. One of the genes that encodes a telomerase subunit does not encode a protein. When the gene for this subunit is transcribed, the result is not an mRNA, but an RNA that functions on its own.

7. Knockout mice can be made that are completely lacking the telomere subunit you discussed in point 6, because the gene for the RNA has been "knocked out." What do you think is the phenotype of these mice?

   After discussing point 7, read the following:

   Mice that are *mtr-/-* are lacking the essential RNA component of telomerase. This component acts as the template for addition of telomeric repeated sequences to the 5' ends of newly replicated DNA, which would otherwise be shortened by the removal of the RNA primer used to start its synthesis. Without the RNA component, telomerase does not work.

   The first generation of *mtr-/-* mice are fine; but after three or four generations of breeding mice with this genotype to each other, the offspring show premature gray hair, loss of hair, impaired healing of wounds, cancer, and shortened lifespan.

8. When the cloned sheep Dolly was born, everyone was curious about how long the telomeres of her cell's chromosomes would be. Why? (Hint: She was cloned from a somatic cell of an adult sheep that was already several years old.)

9. Activation of telomerase in cells that lack it has been suggested as a mechanism for delaying aging or extending lifespan. What is your opinion about this idea? Would it work, in principle? What would be the expected negative consequences?

Source: de Lange and Jacks.1999. *Cell* 98:273.

Topic Packet 3: BRCA and APC

As a team, discuss these points.

1. Start by dividing your team into two sides. Each side will discuss either case a or case b. After a few minutes, each side explains to the other side the situation and the conclusions it reached.
    a. You have a close friend whose paternal grandmother, father, and brother all had colon cancer by age 35. Your friend is worried about his risk for colon cancer and is asking for your advice.
        - Is there a test he can take that will evaluate his risk?
        - What is the test? How often does it have to be administered? Does it require a colon sample, a blood sample, samples from his relatives…?
        - Is there more than one test? If so, what does each measure?

    b. You have a close friend whose grandmother, mother, sister, and aunt (on the maternal side) all had breast cancer by age 40. None of them were genetically tested, but your friend is worried about her risk for breast cancer and is asking for your advice.
        - Is there a test she can take to evaluate her risk?
        - What is the test? How often does it have to be administered? Does it require a sample of breast tissue, a blood sample, samples from her relatives…?
        - Is there more than one test? If so, what does each measure?

2. The colon cancer side reads c below. The breast cancer side reads d below. After a few minutes, each side explains the information to the other side.
    c. Colorectal cancer is the second leading cause of cancer deaths in the U.S. Hereditary colon cancer comes in two forms: FAP (familial adenomatous polyposis) and HNPCC (hereditary nonpolyposis colorectal cancer). Genetic tests are available for the common mutations in these genes. Here is some information about each type of hereditary colon cancer.

    FAP
        - less than one percent of colorectal cancers
        - the inherited mutation is in the APC (adenomatous polyposis coli) tumor suppressor gene
        - causes hundreds of polyps to form in the colon as early as age 10 and almost always by age 35
        - failure to remove the polyps almost always leads to cancer
        - 67 percent of FAP patients who see a doctor about symptoms (diarrhea, rectal bleeding) have cancer
        - if a person tests positive for the mutant APC gene, the recommended course is annual colonoscopy

    HNPCC
        - the inherited mutation is in one of at least five different genes that function in DNA mismatch repair
        - causes colon cancer at an age of onset of about 45
        - lifetime risk of cancer can be as high as 85 percent
        - if a person tests positive for a mutant allele annual, colonoscopy starting at age 20–25 and annually after age 35

Some tests are physical or visual—like digital rectal exams, colonoscopies, and x-rays. Feces can be tested for minute amounts of blood. For those with a family history, blood marker tests and genetic tests may be recommended.

Does this information change or add to the advice you would have given to your friend? How would you summarize this information, and where would you advise your friend to go for more information?

d. Approximately 5–10 percent of breast cancer cases are hereditary, which means that a contributing factor is the inheritance of a mutant gene. The major causes of hereditary breast cancer are mutations in either BRCA1 or BRCA2. In general, a woman's lifetime risk for breast cancer is about 12 percent, but inheriting a mutation in one of these genes increases lifetime breast cancer risk to 40–80 percent.

   Some mutations are more common in certain populations. A woman in a family with a history of breast cancer could be tested for one of these known mutations. However, if the mutant allele is present, it indicates only an increased risk for breast cancer, because not everyone with a mutant allele will develop breast cancer. On the other hand, if no mutant alleles can be detected, it might be because the family has a different mutation than the ones that are normally tested for. Both the BRCA1 and BRCA2 genes are large, so sequencing the entire genes to look for mutations is not commonly done.

   Does this change or add to the advice you would have given to your friend?

3. Would a loss-of-function mutation in APC be dominant or recessive? That is, would a mutation in one copy of an APC gene be sufficient to see the phenotype of increased cancer risk, or would two mutant alleles be necessary? Answer the same question for HNPCC, genes and for BRCA1 and BRCA2.

4. Are the APC, HPNCC, BRCA1, and BRCA2 genes classified as tumor suppressors or as oncogenes? Explain what these classifications are and how genes are put into one category or the other. What was Dr. Mary-Claire King's objection to the "tumor suppressor" categorization? (You can view her interview for the *Rediscovering Biology* project on the video, or read the transcript at http://www.learner.org/channel/courses/biology.)

5. One possibility for people who inherit an allele that increases their risk for a certain type of cancer, like colon or breast cancer, is prophylactic surgery. What do you think this means for colon cancer? What does it mean for breast cancer? Another possibility is prophylactic chemotherapy. What does this mean?

After discussing the question, read the following:

Prophylactic colectomy (removal of colon before cancer develops) is recommended for people with the APC gene only if they have multiple polyps. It is not recommended for people with a family history of HNPCC, or people with the APC gene who do not develop multiple polyps.

Research in 1999 found that prophylactic mastectomy was associated with a 90 percent reduction in incidence in women with a family history of breast cancer. Research in 2001 showed that tamoxifen treatment had little or no effect on women with BRCA1 mutations, but women with BRCA2 mutations had significant benefit.

6. A study in the *Journal of the American Medical Association* found that only 43 percent of family members predisposed to colon cancer because of an HNPCC mutation were likely to get a genetic test to see if they carried the mutant allele. Does this figure seem high or low to you? What factors affect a person's decision to be tested for a gene allele like an APC or HPNCC allele that indicates a high risk for colon cancer, or the BRCA1 or BRCA2 alleles that indicate a high risk of breast or ovarian cancer?
7. In 1994, *Science News* published four real-life ethical dilemmas that genetic counselors had encountered and asked readers for their opinions on the solution. One of the situations was a 30-year-old woman who had been diagnosed with familial adenomatous polyposis (FAP). Doctors and genetic counselors suggested that she inform her siblings and have her children tested. She refused.

   Should the genetic counselors inform the family members of their risk, against the woman's wishes?

After discussing the question, read the following:

> Although the readers who sent in their opinions split 50–50 on whether or not to inform the family, a panel of four genetic counselors and medical ethicists all agreed that the family should be informed, regardless of the woman's stated intentions.

Sources: Rosen et al. 2003. BRCA1 gene in breast cancer. *J. Cell Physiol*. 196[1]:19–41.
http://searchosp1.nci.nih.gov/whealth/whr0001/breast.htm;
http://www.docguide.com/dg.nsf/PrintPrint/2DC8DA5F0525AD7A852567670068BA5D;
http://www.screening-for-colon-cancer.com/index.php3;
http://www.sciencenews.org/sn_edpik/ms_2.htm

Activity 5: The Big Picture

Based on video and online text content

30 minutes

Setup

The overall goal of cancer research has, of course, been to cure cancer. Although Nixon declared war on cancer in 1971, we haven't found a cure. However, we have learned a great deal about the causes of cancer and how to treat it effectively, as well as fundamental principles about cell division, mutation, and gene regulation. As a final wrap-up to this unit, discuss the following questions about the big picture of cancer and cancer research.

Materials

- One copy of the Discussion Questions per person (master copy provided)

Discussion Questions

1. Billions of dollars have been spent on cancer research in the U.S. Just to give you an idea, the National Cancer Institute's 2003 budget was around $4.6 billion. Consider what we have learned about the basic workings of the cell and the function of human genes. Weigh the state of cancer prevention and therapy today against the amount of money we have spent.
    a. In your opinion, has it been worth it?

    b. How much more money and time will it take until cancer is as life-threatening as, say, a bacterial infection that can be treated with antibiotics?

    c. What do you see as the future of cancer research and cancer therapy? What new therapies have you heard about or could you imagine being developed?

    After discussing question 1c, read the following and answer the questions:

    RNA interference, or RNAi, is a mechanism that effectively silences genes completely and with great efficiency. It is found in nearly all organisms—from petunias to worms to mammals. RNAi is initiated by the introduction of double-stranded RNA of a sequence that is designed to target specific genes. The double-stranded RNA triggers a cascade of events, leading to the stimulation of the enzymes Dicer and RISC. These enzymes destroy specific mRNAs, preventing expression of a gene by eliminating any RNA produced from it. So far, interfering RNAs have been able to shut off expression of specific genes in plants, worms, fruit flies, and mammalian cells.

    RNAi has been suggested as a possible therapy for many diseases, including cancer. How might it be used to treat cancer? What information would be needed before RNAi therapy for a specific cancer could be started? What difficulties do you foresee for the development of this treatment?

    d. What is your opinion on the amount of attention and research funds that are spent on cancer, compared to other diseases that we are all concerned about? Compare cancer programs to, for example, emerging or re-emerging infectious diseases such as AIDS and tuberculosis; illnesses of Western cultures, like adult onset-diabetes and obesity; mental illness; or any others you can think of. Where would you allocate funds, if it were up to you?

2. Breast cancer occurs less frequently in African American women than white women (100 cases/100,000 vs. 114/100,000). However, the five-year survival rate for African American women is 69 percent, while for white women it is 84.4 percent.

   In 1996, the colorectal cancer death rate was 16.4 per 100,000 for white Americans and 22.5 per 100,000 for black Americans.

   The death rate for all cancers combined is about 30 percent higher for blacks than for whites.

   a. List factors that might contribute to these disparities.

   b. Of the possible contributing factors you have thought of, how many are biological and how many are societal?

   c. What do you think can be done to correct racial disparity in survival and treatment of any diseases, not just cancer?

3. In your biology classes, have you used cancer as a framework for lessons on, for example, cell division or cell signaling? If so, how have you used cancer examples? Will you change your lessons as a result of what you have learned from this unit? If not, will you be incorporating cancer examples in your lessons?

4. As teachers, we have an opportunity to pass on information about cancer causes and prevention to our students. What do you think is the single most important piece of information you can provide to your students? How can it be presented so it has a lasting impact?

5. As teachers, we process a great deal of information about cancer and carcinogens, from advice presented to the general public, to more specialized information on the biology of cancer. As the result of your reading, have you made (or plan to make) any lifestyle changes, with the goal of reducing your own risk for cancer?

Sources: http://cis.nci.nih.gov/fact/1_1.htm;
http://www.nature.com/horizon/rna/background/interference.html

Notes