HOW TO USE THIS RESOURCE
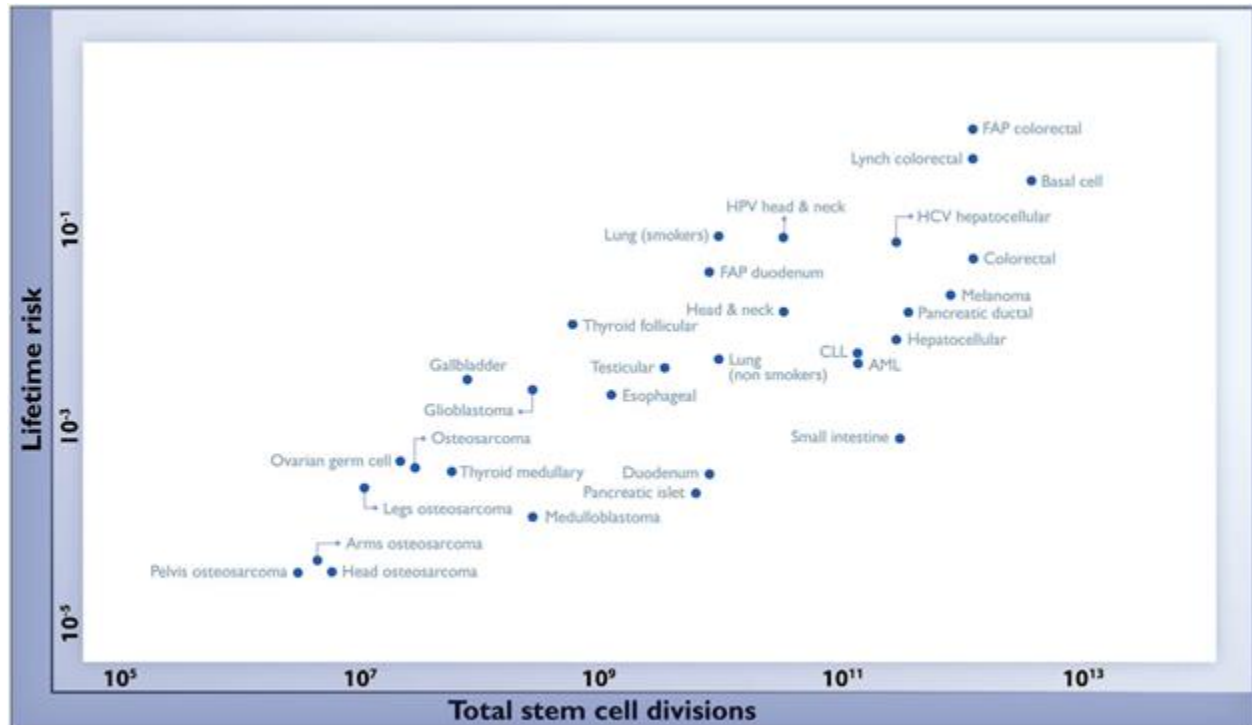
Show the figure below to your students along with the caption and background information. The "Interpreting the Graph" and "Discussion Questions" sections provide additional information and suggested questions that you can use to guide a class discussion about the characteristics of the graph and what it shows.

FAP = Familial Adenomatous Polyposis ◆ HCV = Hepatitis C virus ◆ HPV = Human papillomavirus ◆ CLL = Chronic lymphocytic leukemia ◆ AML = Acute myeloid leukemia

Caption: Relationship between the risk of cancer and the number of times stem cells divide in different types of body tissue over the course of a person's lifetime. Lifetime risk (y-axis) is expressed as the base 10 logarithm of the probability of developing cancer, where 10^{-1} is 10% risk, 10^{-2} is 1% risk, and so forth.

BACKGROUND INFORMATION

Cancer is typically attributed to hereditary and environmental factors, but these only explain a fraction of overall cancer risk. These factors fail to explain why some of the body's tissue types are more likely to develop cancer than others even in cases where hereditary and environmental risks are equal. For example, tissues of the small and large intestine are both susceptible to cancer caused by mutations in the *APC* gene, which regulates the production of the APC protein, a tumor suppressor that keeps cells from dividing in an uncontrolled way. The small and large intestines are presumably exposed to the same environmental factors, and yet cancer of the colon (part of the large intestine) is far more common than cancer of the duodenum (part of the small intestine). In this study, researchers investigated how a third factor—chance genetic mutations that occur during stem cell division—may contribute to the overall rate of cancer incidence in each tissue. The researchers plotted data from previously published studies to determine whether tissues with a greater number of stem cell divisions (and therefore a greater amount of DNA replication) over a person's lifetime is related to the overall risk of cancer in that tissue.

INTERPRETING THE GRAPH

The 31 different cancers represented in this figure were chosen because reliable data existed in the literature on two variables: lifetime (80 years) risk of cancer and the total number of stem cell divisions that occur in that tissue during a lifetime. Lifetime risk is shown on the *y*-axis axis and is expressed as the base 10 logarithm of the probability of a person developing the cancer. For example, a lifetime risk of 10^{-2} is a 1% lifetime risk. Therefore, the risk of a person developing thyroid cancer over the course of an 80-year lifespan is about 1 in 100.

The *x*-axis shows the estimated total number of stem cell divisions within a particular tissue type beginning with the first precursor cells. This number was calculated based on the total number of stem cells in the developed tissue and the rate of normal cell turnover within that tissue. The researchers focused on stem cells because most fully differentiated cells are short-lived and are therefore unlikely to produce cancerous cells.

Colorectal and duodenal cancers are each represented as two data points, one of which begins with the letters FAP, which stands for familial adenomatous polyposis. FAP is a genetic condition that causes polyps to form in the colon which, if left untreated, have a very high chance of leading to cancer. The data points for each set of FAP and non-FAP cancers align vertically because stem cell divisions are based on the same underlying tissue types; however, the lifetime risk will be higher for patients with FAP because this genetic condition adds to the risk above environmental factors and chance mutations.

To determine whether a correlation exists between lifetime cancer risk and the number of stem cell divisions, the researchers performed two statistical analyses: Spearman's rho and Pearson's r.

Spearman's rho ranks each set of values from high to low and then calculates a correlation value, with 1 being a perfect positive correlation. The variables in this figure have a Spearman's correlation of 0.81 with a *p*-value of 3.5×10^{-8}, which means that the two variables are positively correlated and the correlation is statistically significant. Pearson's r is very similar, but it assumes that the relationship between the two variables is linear, so while it is commonly used, it may not be ideal for this nonlinear relationship. However, it gives about the same result: a correlation of 0.804 with a *p*-value of 5.15×10^{-8}.

Both analyses indicate a significant positive correlation between cancer risk and the number of stem cell divisions in a given tissue. This correlation accounts for approximately 65% of the variation in cancer incidence among tissue types, which is simply the square of the Pearson's correlation coefficient. In other words, the "bad luck" of random mutations that occur during normal cell division accounts for about two-thirds of the variation in cancer risk among tissues, while hereditary and environmental factors account for the remaining one-third.

Teacher Tip: Prompt your students to explain the parts of the graph as applicable:
- Graph Type: Scatter plot
- *X*-axis: Total stem cell divisions within the tissue affected by a particular cancer throughout a lifetime
- *Y*-axis: Lifetime risk of developing a certain cancer

DISCUSSION QUESTIONS
- What trends do you notice in this figure?
- What do the trends in this figure tell you about the relationship between stem cell divisions and cancer?
- What are the lifetime risks (expressed as %) of colorectal cancer and duodenal cancer (not the FAP versions)? What is a possible explanation for the difference in lifetime risk?
- Why do you think researchers focused on stem cells rather than fully differentiated cells?

- Compare the risk of bone cancers (osteosarcomas) to the risk of basal cell cancer (also known as basal cell carcinoma). Based on prior knowledge or research, why do you think sarcomas are less common than carcinomas?
- According to the National Cancer Institute (https://seer.cancer.gov/statfacts/html/breast.html), the lifetime risk of developing breast cancer is about 12% for women. The most common type of breast cancer is invasive ductal carcinoma (IDC) and accounts for 80% of all breast cancers. Without knowing anything about stem cell division in this type of tissue, where would you expect to find the data point for IDC and why?
- Explain why the lung cancer (smokers) and lung cancer (nonsmokers) data points are vertically aligned.
- How much higher is the risk of lung cancer in smokers than in nonsmokers?
- Based on the data in this figure, would you expect the risk of cancer to increase or decrease as a person gets older? Why?

SOURCE

Figure 1 from:

Cristian Tomasetti and Bert Vogelstein. Variation in cancer risk among tissues can be explained by the number of stem cell divisions. 2015. *Science* 347 (6217), 78-81.

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