Understanding Cancer Risk

Research Advocacy Network

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Introduction

Cancer risk is a multi-faceted concept. To someone who has never had cancer, risk may mean the likelihood of developing cancer in the future. To someone who has been successfully treated for cancer, risk may mean the chance that the cancer will recur over time. Someone facing cancer treatment may be interested in the risk that the cancer will spread, the risk of experiencing a certain side effect or toxicity, as well as the risk vs. benefit trade-offs of various treatment regimens.

In this document, we consider several different aspects of cancer risk. The first chapter describes risks associated with developing cancer and the influence that factors like our genes and lifestyles have on those risks. The second chapter discusses risks related to cancer treatment. All cancer treatments have side effects and certain patients are more prone to these than others. In some cases, biomarkers have been discovered that can help determine a patient's risk for side effects, and we discuss these examples. We also consider the risk of side effects vs. treatment benefits and how patients weigh these two opposing forces in making treatment decisions.

The third chapter focuses on risk of cancer recurrence. We begin by describing some general factors associated with recurrence risk. For some types of cancers, risk of recurrence can be predicted by tests that examine our genes. We discuss these tests, what they measure, and how they are used in clinical practice.

The fourth chapter explores patient perceptions of cancer risks, including risk of developing cancer, cancer recurrence, and risks associated with metastatic cancers. We examine risk-benefit trade-offs and how factors such as family history, culture, and life stage may influence these perceptions. Ultimately, our perceptions influence our treatment decisions—an idea that we discuss in the context of published research findings.

Chapter 5 describes some of the most commonly used means of presenting numeric risk information. We often hear risk factors described in terms of numbers such as, "this gene increases cancer risk by 10%" or "exercise reduces the risk of cancer by 20%." We explore these numeric aspects of risk in an attempt to better understand, and eventually better portray, the likelihood of cancer risk numbers for patients. We also describe some of the methods used to portray risk in research results.

In the sixth chapter, we consider cancer risk communication. We discuss the benefits of verbal versus numeric descriptions of risk, some steps and tools designed to promote better physician/caregiver communication with patients about cancer risks, and how physician perceptions of risk can influence risk communication to patients.

The last chapter considers ways that this information may be useful to advocates. It is clear that patients do not always understand cancer risk numbers and advocates may be interested in working to improve this situation. How can we, as advocates, promote communication among patients, healthcare providers, and even researchers that accurately portrays risk in a way that patients understand? What questions should patients ask to help them better understand risk? We explore these questions and consider some ideas for advocates to contemplate.

Chapter 1: Risk of Developing Cancer

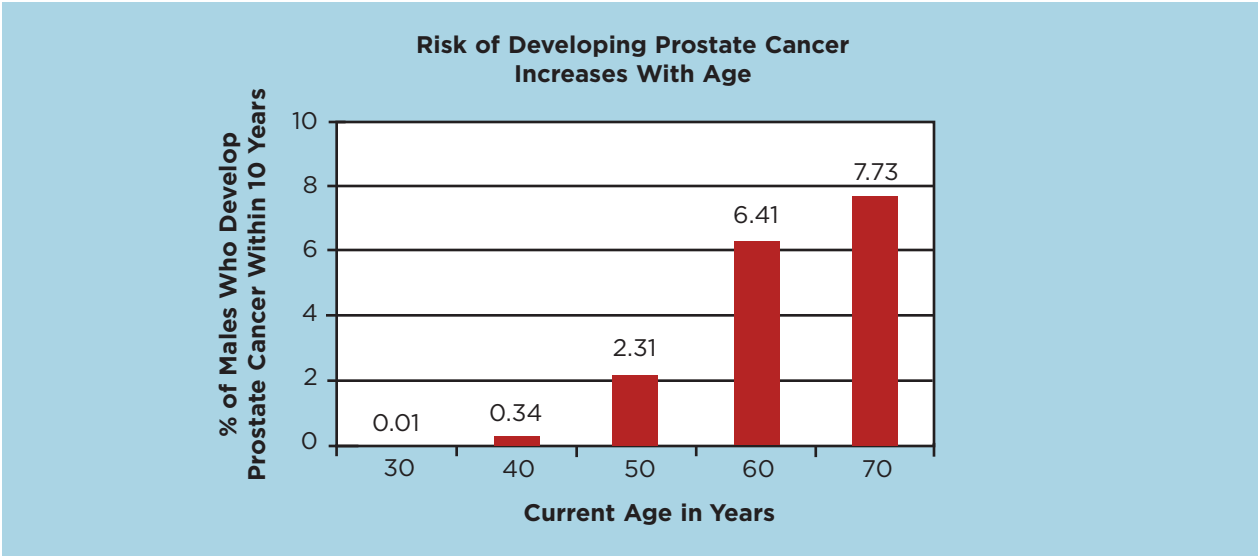
Many factors can influence our risk of developing cancer. Most of these factors, such as genes, smoking, exercise, and being overweight do not directly cause cancer, but rather increase our chances of developing cancer. Some of these risk factors are things we can control, whereas others are not. Additionally, the link between risk factors and cancer may range from mild to strong. An example of a strong risk is the link between smoking and lung cancer—people who smoke are 15 to 30 times more likely to develop lung cancer and die from the disease than nonsmokers. An example of a more modest cancer risk is being male—males are about 1.3 times more likely than females to develop some type of cancer in their lifetimes. In some cases, the link between a risk factor and cancer is equivocal, meaning that some studies show a link and others don't. As a result, we can't say for sure whether the proposed risk factor really increases the risk of cancer.

In this chapter, we examine some of the factors that affect cancer risk, including general factors, environmental and lifestyle factors, and genetic factors. We also consider how genes and our environment interact to cause cancer—an active area of research that is beginning to provide some answers as to why some people are more likely to get cancer than others.

Factors that Affect Cancer Risk

General Factors

Age is one of the main factors associated with cancer risk. As age increases, so does the risk of most cancers. The relationship between many different types of cancers and age is tracked by the National Cancer Institute in a program known as Surveillance Epidemiology and End Results (SEER). Data for each cancer type and age group can be found on their Web site: http://seer.cancer.gov/faststats.



This graph shows the percentage of males who are expected to develop prostate cancer within 10 years of their current age. Among those who are age 30 now, only 0.01% are expected to develop cancer within 10 years. Of those who are age 50 now, slightly more than 2% are expected to develop cancer within 10 years. Among those who are age 70 now, nearly 8% are expected to develop prostate cancer within 10 years. Data from the Centers for Disease Control and Prevention. Available at: www.cdc.gov/cancer/prostate/statistics/age.htm. Accessed March 24, 2014.

Certain types of viruses and bacteria also increase the risk for different cancers. For example, human papilloma virus is a risk factor for cervical cancer and the bacteria Helicobacter pylori is a risk factor for stomach cancer.

Risk factor: anything that increases the likelihood that a person will develop cancer.

VIRUSES THAT ARE RISK FACTORS FOR CANCER

Virus	Type of Cancer
Epstein-Barr virus	Burkitt's lymphoma
Human papillomavirus*	Cervical cancer
Hepatitis B virus	Liver cancer
Human T-cell lymphotrophic virus	Adult T-cell leukemia
Kaposi-s sarcoma-associated herpesvirus*	Kaposi's sarcoma

*Note that there is no space between the word virus and genus names such as papilloma or herpes.

Table information from National Cancer Institute. Understanding cancer. Available at: www.cancer.gov/cancertopics/understandingcancer/cancer. Accessed April 27, 2013.

Inherited Genes

Variations or mutations in our genes can affect cancer risk. Most of the genetic mutations observed in cancers are not inherited, but rather develop over the course of an individual's life based on his or her interactions with the environment (for example, smoking and sunlight can both cause mutations). However, some gene mutations are inherited and, consequently, the cancers with which they are associated tend to run in families. These genetic mutations can be carried and transmitted to their children by men or women. Examples of these inherited conditions are listed in the following table.

EXAMPLES OF INHERITED MUTATIONS THAT INCREASE CANCER RISK

Name of Condition	Gene(s) Affected	Type of Cancer
Hereditary breast and ovarian cancer syndrome	BRCA1, BRCA2	Breast, ovarian
Cowden syndrome	PTEN	Breast, uterus, thyroid
Hereditary non-polyposis colorectal cancer syndrome (Lynch syndrome)	DNA mismatch repair genes (MLH1, MSH2, MSH6, PMS2)	Colorectal, endometrial
Familial adenomatous polyposis	APC	Colorectal
Li-Fraumeni syndrome	TP53	Soft tissue sarcomas (tumor in fat, muscle, nerve, joint, blood vessel, bone, or deep skin), breast, leukemia, lung, brain, adrenal

Table information from American Society of Clinical Oncology. Cancer.Net. Available at: www.cancer.net. National Cancer Institute. Understand Cancer Series. Available at: www.cancer.gov/cancertopics/understandingcancer/cancergenomics/allpages. Accessed April 24, 2013.

Although we don't know how to prevent cancer in those who have inherited mutations, more frequent cancer screening may help detect the disease early when treatment is more effective. Moreover, inherited mutations increase a person's risk for cancer, but not everyone with a genetic mutation will actually develop cancer.

As research techniques become more sophisticated, investigators are uncovering additional gene variations that increase a person's risk for cancer. However, the increase in risk that results from these genetic variations is typically quite small. Researchers are now seeking to determine how inherited genetic variations combine with environmental or lifestyle factors to increase the risk of cancer. Another line of research is to evaluate the effects of multiple gene variations—a sort of gene profile that may explain a greater proportion of cancer risk.

Environmental and Lifestyle Factors

A number of factors in our environment can increase the risk of cancer, as can certain behaviors that are generally considered under the heading "lifestyle" factors. Examples include obesity, physical inactivity, tobacco exposure, chemicals such as benzene and arsenic, and excessive or prolonged exposure to radiation in the forms of sunlight and x-rays. More information about these risk factors and the cancer to which they have been linked is available from the National Cancer Institute at the following Web site: www.cancer.gov/cancertopics/pdq/prevention/overview/patient/page3.

EXAMPLES OF ENVIRONMENTAL AND LIFESTYLE RISK FACTORS FOR CANCER

- Cigarette smoking and tobacco use
- Radiation (including radon, a radioactive gas)
- Immunosuppressive medicines
- Diet
- Alcohol
- Physical inactivity
- Obesity
- Environmental chemicals (arsenic, secondhand smoke, outdoor air pollution)

These environmental and lifestyle factors can influence cells, eventually causing mutations or changes in our DNA. These mutations may alter the ability of our genes to carry out their functions, resulting in an increased chance of cancer.

However, it is important to note that having one or more risk factors does not necessarily mean that someone will develop cancer. We all know people who have one or more risk factors and never develop cancer, such as the woman who smoked a pack of cigarettes a day for 50 years and died at age 90 of complications related to old age—not lung cancer. For reasons that we are only beginning to understand, some people are more sensitive than others to certain risk factors.

Combination of Inherited Genes and Environmental Factors

Researchers have long believed that most cancers are caused by an interaction between genes and environment, instead of either one of these factors alone. Unfortunately, studying these interactions has been extremely difficult, in part because of the difficulties identifying and measuring environmental factors.

One example of a study that found interactions between genes and environment in cancer was conducted by a group of researchers from Vanderbilt University in Nashville, Tennessee. Dr. Zheng and colleagues examined the link between well-done red meat and colorectal polyps, which can be precursors to colorectal cancer. It has long been known that certain chemicals in well-done meat can act as carcinogens, increasing the risk of colorectal cancer. The researchers collected information on the amount of red meat eaten by participants, how the meat was cooked, and its degree of doneness. They also calculated a score for each participant based on 16 variations in their genes that had to do with metabolizing certain known carcinogens in well-done meat. Participants were classified into different groups based on their genetic variation scores. Results showed that high red meat intake was associated with an increased risk of colorectal polyps and that this risk depended on the genetic variations. Although the investigators caution that this study is not conclusive — it needs to be replicated in a larger population — it does provide an example of how gene-environment interactions are being studied in cancer.

Which Genes Are Risk Factors for Cancer?

Certain genes in our bodies are involved in critical biological processes that our cells need in order to replicate themselves or repair DNA. When these genes are altered, either due to inherited mutations or mutations acquired during our lives, they may not be able to perform their normal function(s). Conversely, some of the genes may become overactive and perform their functions too aggressively. Three of the most important types of genes that are risk factors for cancer include tumor suppressor genes, oncogenes, and DNA repair genes.

Tumor Suppressor Genes

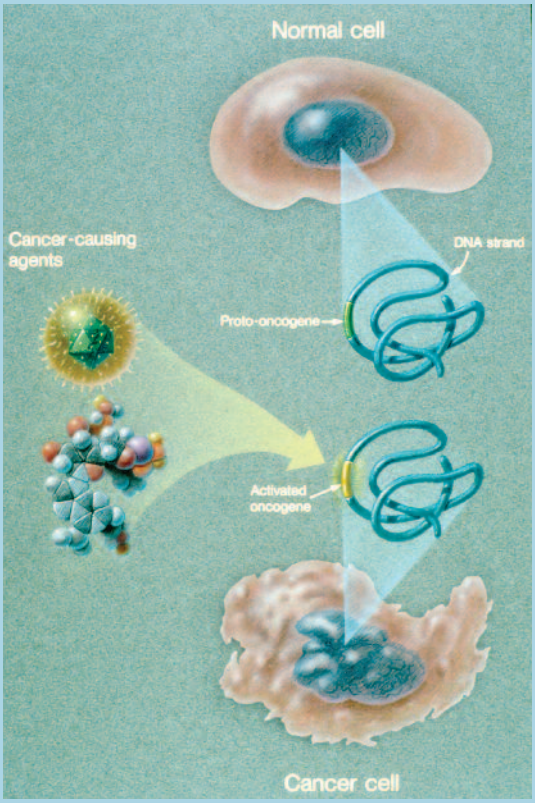
Tumor suppressor genes help limit cell growth through a variety of processes. Mutations in these genes can interfere with their normal function, which is to help prevent cells from proliferating out of control. Examples of tumor suppressor genes are BRCA1 and BRCA2; some inherited mutations in these genes can increase the risk of breast, ovarian, and other cancers such as pancreatic cancer and testicular and prostate cancers in men. Another example of a tumor suppressor gene is known as p53. Mutations in p53 are typically acquired rather than inherited. In fact, the p53 gene is mutated or absent in an astounding 50% of all cancers.

Oncogenes

Oncogenes are genes whose presence can lead to cancer. Oncogenes are variations of normal genes known as proto-oncogenes that help regulate cell growth. For example, growth factors, growth factor receptors, intracellular signaling molecules, and proteins that bind to genes to start transcription are all examples of proteins encoded by proto-oncogenes. When proto-oncogenes are mutated or otherwise altered, it can lead to the uncontrolled cell growth that characterizes cancer.

ONCOGENES DEVELOP FROM PROTO-ONCOGENES

A proto-oncogene in a normal cell appears to regulate and influence cell growth and division. When a cancer causing agent affects a cell's DNA and the oncogene is activated, cancer can develop.



Graphic credit: Jane Hurd, Illustrator. National Cancer Institute (www.cancer.gov), NCI Visuals Online (http://visualsonline.cancer.gov/).

DNA Repair Genes

Mistakes during DNA copying or replication are common and the normal role of DNA repair genes is to fix these mistakes. Mutations in DNA repair genes can prevent these fixes, which can eventually lead to cancer. Mutations in DNA repair genes may be acquired or inherited, as is the case in Lynch syndrome or hereditary non-polyposis colorectal cancer.

For more information on how mutations alter DNA to increase the risk of cancer, you may want to visit the National Cancer Institute's Understanding Cancer Web site: http://cancer.gov/cancertopics/understandingcancer.

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Chapter 2: Risks Related to Cancer Treatment

Amanda has been diagnosed with cancer and is trying to decide between two treatment options. The effectiveness of the treatments is similar, but the potential side effects are different. One of the treatments has a higher risk of nerve damage that could be painful. The other treatment has a higher risk of nausea, vomiting, and skin rash. Unfortunately, no information is available that would help Amanda determine whether she is at greater risk for one side effect or the other.

As shown in this example, cancer treatments are associated with side effects that must be weighed against the potential benefits when making treatment decisions. In our example, the decision is simplified somewhat by the equal effectiveness of the two treatments. However, in real life, this is seldom true. Most often, we are making decisions about treatments that have different levels of effectiveness, as well as different side effects. In this brief chapter, we consider some of the risks related to cancer treatment.

Biomarkers for Side Effects/Toxicities

In some cases, a person's risk of experiencing a side effect or toxicity in response to cancer treatment can be predicted based on his or her genes. This type of analysis falls under the heading of pharmacogenomics, or the study of how a person's genes influence his or her response to drugs. Scientists have found that the DNA sequence of a person's genes can affect how he or she breaks down or metabolizes drugs, which can influence the intensity of side effects. To date, only a few of these gene sequences have been identified, but research is proceeding in this area with the goal of matching patients with the treatments to which they are best suited — the ones that provide the greatest benefit with the lowest risk of side effects.

Toxicity: the extent to which something is poisonous or harmful

Side effect: a peripheral or secondary effect, especially an undesirable secondary effect of a drug or therapy

For more information on biomarkers, you may want to download Research Advocacy Network's tutorial on Biomarkers in Cancer, available at: http://researchadvocacy.org/index.php?/general-resources/publications/.

Chemotherapy With 5-Fluorouracil (5-FU)

Fluorouracil or 5-FU is a chemotherapy drug that may be used to treat a variety of different cancers, including breast cancer, colorectal cancer, gastric cancer, pancreatic cancer, and others. Some people have genetic variations that interfere with the metabolism of 5-FU. If you have one of these genetic variations, you are at increased risk for toxicities associated with 5-FU. These toxicities or side effects include neutropenia (low white blood cell count), diarrhea, hand-foot syndrome (pain, swelling, and/or redness of the hands or feet), stomatitis (inflammation or irritation of the mucous membranes in the mouth), mucositis (lining of the digestive system becomes inflamed, can include mouth sores), and myelosuppression (reduced blood cells and platelets). This is because the genes encode proteins that help metabolize 5-FU. If the genes have certain variations in them, the proteins produced from the genes may not function correctly and therefore cannot efficiently break down the drug. As a result, the drug builds up in the body. Increased levels of the drug are more likely to cause toxicities.

Neutropenia: low white blood cell count

Variations in at least three different genes can interfere with 5-FU metabolism: the TYMS gene that encodes an enzyme known as thymidylate synthase (TS), the MTHFR gene that encodes the protein methylenetetrahydrofolate reductase, and the DPYD gene that encodes the protein dihydropyrimidine dehydrogenase (DPD). Laboratory tests are available to examine the genes associated with 5-FU metabolism.

Chemotherapy With Thiopurines

Thiopurines are a group of chemotherapy drugs that include azathioprine (AZA), 6-mercaptopurine (6-MP) and thioguanine (6-TG). Some brand names for these drugs are Azasan®, Imuran®, and Purinethol®. These drugs may be used to treat some types of leukemia. An enzyme known as thiopurine S-methyltransferase (TPMT) is partly responsible for metabolizing thiopurines.

Hand-foot syndrome: pain, swelling, and/or redness of the hands or feet

Some variations in the gene that encodes the TPMT enzyme reduce a person's ability to metabolize thiopurine drugs. One out of every 10 people in the population has a genetic variation that reduces the enzyme's activity to 50% of normal. One in 300 people has absolutely no TMPT enzyme activity. If someone with no TMPT enzyme activity is given normal doses of thiopurines, he or she could die because the drugs become too highly concentrated in the body. In some cases, these people can tolerate very low doses of thiopurines. People with variations in TMPT that reduce but do not eliminate enzyme activity can usually safely tolerate lower doses of thiopurines.

Stomatitis: inflammation or irritation of the mucous membranes in the mouth

It is interesting to note that some people have very high levels of TPMT activity and may inactivate thiopurines before the drugs can act. These people may be less likely to exhibit a clinical response to thiopurines and may be better served to select a different drug. Laboratory tests are available to examine the TMPT gene.

Chemotherapy With Irinotecan

Another example of a genetic variation that can influence drug metabolism involves a chemotherapy drug called irinotecan that is used to treat some types of colorectal cancer and other cancers. Irinotecan is metabolized by enzymes known as the UGT1A enzymes. Individuals with certain variations in the UGT1A enzyme cannot break down irinotecan as efficiently as others, and may develop toxicities or side effects such as diarrhea and low blood cell counts as levels of the drug accumulate in the body. Laboratory tests are available to examine the UGT1A gene.

Mucositis: inflammation of the lining of the digestive system

Long-Term Risks of Cancer Treatments

When considering side effects of treatment, we tend to be most concerned with those that are likely to occur now or in the near future. We tend to think less about those that may occur in the distant future. However, chemotherapy, surgery, and radiation therapy may also be associated with long-term side effects, often referred to as late effects because they may occur long after the therapy is complete.

Myelosuppression: reduced blood cells and platelets

Late effects: side effects of cancer treatment that appear after treatment has ended

Late effects of cancer therapy depend on the location of cancer and type of treatment, as well as some unpredictable factors associated with the individual. Each person's experience is somewhat unique: Some individuals may experience many late effects, whereas others may experience only a few or a single late effect. Some may not experience any late effects.

EXAMPLES OF LATE SIDE EFFECTS WITH DIFFERENT CANCER THERAPIES

Type of Cancer Therapy	Examples of Late Side Effects*
Chemotherapy	Early menopause, Heart problems, Infertility, Liver problems, Lung disease, Osteoporosis, Reduced lung capacity, Increased risk of other cancers
Radiation therapy	Cataracts, Cavities and tooth decay, Heart problems, Thyroid problems Infertility, Lung disease, Intestinal problems, Memory problems, Osteoporosis, Increased risk of other cancers
Surgery	Lymphedema (lymph fluid buildup in arms or legs), Pain, Infection

*Not all patients will experience these side effects. The risk of side effects depends on the location of the cancer and the type of treatment. For example, not all chemotherapies have infertility as a possible side effect.

Modified from Mayo Clinic. Cancer survivors: Late effects of cancer treatment. Available at: www.mayoclinic.com/health/cancer-survivor/CA00073/NSECTIONGROUP=2. Accessed April 29, 2013.

Childhood cancers may lead to additional late side effects (i.e., months or years later) because children are undergoing rapid growth of bones, tissues, and organs at the time of treatment. Cancer therapy can interfere with these processes and lead to late side effects, although not all people who were treated for childhood cancer will experience these.

POSSIBLE LATE EFFECTS (MONTHS OR YEARS LATER) IN INDIVIDUALS TREATED FOR CHILDHOOD CANCER

- Heart problems, including an increased risk of heart attacks
- Blood vessel problems, including an increased risk of stroke
- Lung problems, which can cause difficulty breathing
- Liver problems
- Kidney problems
- Bone problems, such as bone thinning (osteoporosis) and joint pain
- Short stature, caused by slow bone growth
- Obesity
- Infertility
- Memory problems and learning disabilities
- Vision loss
- Hearing loss
- Increased risk of other types of cancers

From Mayo Clinic. Cancer survivors: Late effects of cancer treatment. Available at: www.mayoclinic.com/health/cancer-survivor/CA00073/NSECTIONGROUP=2. Accessed April 29, 2013.

Adjuvant! Online: A Tool To Help Healthcare Professionals Assess Patient Risk

A number of different decision tools exist to assist cancer patients and their physicians in their assessment of risks. One in particular that focuses on risks associated with breast cancer treatment is known as Adjuvant! Online (www.adjuvantonline.com/index.jsp). Adjuvant! Online was designed to help healthcare professionals and patients with early breast cancer discuss the risks and benefits of additional therapy after surgery. The name Adjuvant! refers to adjuvant therapy such as chemotherapy, hormone therapy, or radiation therapy that is given after surgery as a supplement to improve treatment benefit or reduce the risk of breast cancer recurrence.

Adjuvant therapy: additional cancer treatment given after the primary treatment to lower the risk that the cancer will come back.

With Adjuvant! Online, healthcare professionals input information based on an individual patient's age, tumor size, involvement of lymph nodes, tumor grade, and other factors. The software program then provides output in the form of graphics and text related to the patient's risks without adjuvant therapy (risk of relapse and death), reduction of these risks with adjuvant therapy, and the risks of side effects associated with adjuvant therapy.

It should be noted that Adjuvant! Online is designed for use by healthcare professionals who are experienced in oncology. The reason for this is that information about tumor size and margins can be complex and difficult to interpret; incorrect entry of these inputs can result in vastly different risk estimates. However, the results that the program generates are meant to be accessed by healthcare providers who can then discuss them with their patients to assist in treatment decision making.

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Chapter 3: Risk of Recurrence

When considering which type of treatment to undergo for his colorectal cancer, Ben was concerned about the possibility of recurrence. His doctors believed that they could remove all of the cancer with surgery, but Ben—the father of two children under age 16—wanted to minimize the chance that the cancer would return. Ben consulted with his doctors, who suggested that a variety of factors could help estimate the likelihood of tumor recurrence after surgery. This information helped Ben, his family, and his healthcare team decide which type of treatment to pursue once surgery was complete.

In this chapter, we discuss several concepts related to the risk of recurrence, including the factors that influence recurrence and tests that help predict recurrence for some cancers.

General Factors That Influence Recurrence

We are not good at estimating an individual's risk of recurrence for most cancers. Fortunately, this is an active area of research and we are learning more every year. Ideally, we would like to be able to estimate each person's risk of recurrence quickly and accurately so that treatment can be tailored to match. Although progress is being made in this direction, much remains to be discovered, and we must often rely on our knowledge of a person's general risk factors in order to evaluate risk of recurrence.

In general, if a person has risk factors for cancer that do not change after developing cancer, he or she is at a higher risk for recurrence than those without the risk factors. An example is tobacco use. Smoking and other tobacco products are associated with many different types of cancer, including lung, mouth, lip, esophagus, bladder, and stomach cancers. Tobacco use continues to be a risk factor for cancer recurrence after a person has survived one round of cancer, although a person can lower this risk by quitting the habit.

Inherited genetic risk factors do not change after a person has been successfully treated for cancer, and therefore people with these risk factors remain at a higher risk of cancer recurrence than those without the inherited factors. Individuals who are obese are at increased risk of recurrence for breast, prostate, and colorectal cancers. In some cases, such as childhood cancers, treatment of the primary cancer with radiation can increase the risk for cancer recurrence or for a second type of cancer.

Risk of recurrence has been better studied in breast cancer than in many other cancer types. As a result, we know some of the general risk factors associated with breast cancer recurrence. These factors include lymph node involvement, larger tumor size, the presence of cancer cells on the border of the tumor that has been removed, a close margin between the tumor and normal cells, lack of radiation following lumpectomy, younger age, and inflammatory breast cancer. These factors increase the risk of cancer recurrence, but do not guarantee that cancer will return. Each person's situation is different, based on different genomics and different lifestyle factors.

SOME GENERAL FACTORS ASSOCIATED WITH RISK OF BREAST CANCER RECURRENCE

Risk Factor	Explanation
Cancer present in lymph nodes	Risk is increased if cancer is present in lymph nodes at the time of the original cancer diagnosis; involvement of many lymph nodes is associated with higher risk
Large tumors	Risk is increased if original tumor is larger than 5 cm (about 2 inches)
Tumor margins positive for cancer or tumor margins close to cancerous area	Risk is increased if the area around the border of the tumor that has been surgically removed is positive for cancer or if the margin between the tumor and the normal tissue is close
Lack of radiation following lumpectomy	Risk of in-breast recurrence is increased for women who have a lumpectomy to remove their tumor but do not have subsequent radiation (i.e., radiation following lumpectomy is generally recommended)
Younger age	Risk is increased for women who are younger at the time of original diagnosis, especially <35 years of age
Inflammatory breast cancer	Risk is increased for those with inflammatory breast cancer

Table information from Mayo Clinic. Recurrent breast cancer. Risk factors. Available at: www.mayoclinic.com/health/recurrent-breast-cancer/DS01078/DSECTION=risk-factors. Accessed May 2, 2013.

Tests That Help Predict Risk of Recurrence

In an attempt to improve our ability to predict the risk of cancer recurrence, researchers have begun looking at the genes expressed by cancer cells. Several different types of tests are now available that examine a person's genomics to determine his or her specific risk for recurrence.

Oncotype DX®

Oncotype DX® is a genomic test that examines a panel of genes to give a Recurrence Score ranging from 0 to 100 that can help determine the likelihood that an individual's cancer will recur. The types of cancers for which this test can be used are as follows:

- Early stage invasive breast cancer, estrogen receptor-positive, human epidermal growth factor 2 (HER2)-negative
- Ductal carcinoma *in situ* (DCIS) treated by local excision, with or without tamoxifen treatment
- Stage II colon cancer
- Prostate cancer

More information is available at the following Web site: www.oncotypedx.com/.

MammaPrint®

MammaPrint® is a genomic test that examines 70 different genes to categorize a woman as low risk or high risk of distant recurrence of breast cancer. This test can be used for the following types of cancer:

- Stage 1 or 2 invasive breast cancer, with tumor size < 5 cm, lymph node negative, estrogen receptor positive or negative

More information is available at the following Web site: www.agendia.com/pages/about_mammaprint/75.php.

Prolaris®

Prolaris® is a genomic test that examines 46 different genes involved in the cell cycle to give a Cell Cycle Progression (CCP) score that can help predict the risk of recurrence of prostate cancer within 10 years. The test classifies men as low risk, intermediate risk, or high risk. This test can be used for men following prostatectomy (surgical removal of the prostate). More information is available at the following Web site: www.prolaristest.com/.

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Chapter 4: Patient Perception of Risk

Jim and Stan, both men in their mid-50s, have just been to their physician for an annual check-up. They were given the same information sheet describing health issues facing men of their age. The sheet mentions that the risk of prostate cancer increases as men get older and indicates a need for routine screenings. Jim takes the information in stride and vows to schedule a screening next year. Stan, however, becomes extremely worried about his risk of prostate cancer. He schedules a screening exam as soon as possible and, even when his doctor tells him that he doesn't have prostate cancer, he continues to worry that they have missed something. Why do these two men react so differently to the same information?

In this chapter, we consider some of the factors that affect patient perception of cancer risks, including the risk of developing cancer, the risk of recurrence, and risk-benefit trade-offs in cancer treatment decision making.

Perception of the Risk of Developing Cancer

Understanding how people perceive their risk of developing cancer is increasingly important today given the availability of preventive surgeries for several different cancer types. People whose risk of cancer is very high may opt to undergo these procedures if they accurately perceive their risk as high. Conversely, people whose risk of cancer is low may be spared worry and concern over cancer if they accurately perceive their risk as minimal.

As shown in the example of Jim and Stan, people may react differently to the same risk information—emotionally and in terms of health behaviors such as screenings. The following examples outline some studies that investigated various features of risk perception related to the development of cancer. For more details on these studies, visit the Web site at the address provided.

STUDY: Perceived risk of prostate cancer among African-American men

- ***Population studied:*** 88 men with self-reported, first-degree family history of prostate cancer and 120 men without a family history of prostate cancer.
- ***Research question:*** How do African-American men with a family history of prostate cancer perceive their risk of the disease compared with African-American men without a family history of prostate cancer?
- ***Findings:*** Although men with a family history of prostate cancer are twice as likely as those without a family history of prostate cancer to develop the disease, no difference was found between the two groups in their risk perceptions. That is, men with and without a family history of prostate cancer perceive their risks of developing prostate cancer to be similar.
- ***Conclusion:*** The results do not support the hypothesis that family history is associated with an increase in perceived risk of prostate cancer.
- ***Citation:*** Bloom JR, Stewart SL, Oakley Girvan I, Banks PJ, Chang S. Family history, perceived risk, and prostate cancer screening among African American men. *Cancer Epidemiol Biomarkers Prev.* 2006 Nov;15(11):2167-73.

STUDY: Perceived risk of breast cancer among women at average and increased risk

- ***Population studied:*** 1700 women 40-74 years old without a history of breast cancer.
- ***Research question:*** How accurately do women without breast cancer perceive their risk of developing breast cancer?
- ***Findings***

Overall, African American women were less likely than white women to accurately perceive their risk.

What Percentage of Women at NORMAL Risk for Breast Cancer Accurately Perceived That Risk?

Factors associated with overestimating risk: younger age, family history of breast cancer, no children, frequent exposure to media information about breast health.

What Percentage of Women at HIGH Risk for Breast Cancer Accurately Perceived That Risk?

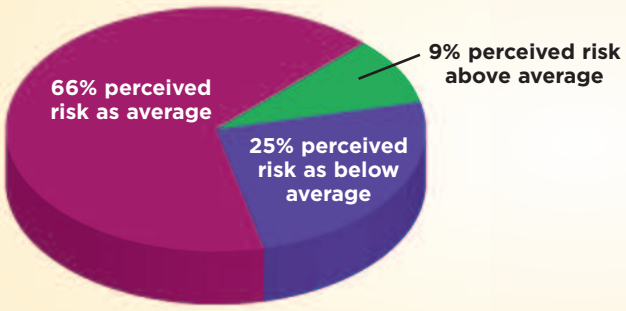
Factors associated with accurate risk perception: younger age, family history of breast cancer.

- ***Conclusion:*** "A majority of women at high risk of developing breast cancer underestimate their risk and a substantial proportion of women at average risk perceive they are at increased risk."
- ***Citation:*** Haas JS, Kaplan CP, Des Jarlais G, Gildengoin V, Perez-Stable EJ, Kerlikowske K. Perceived risk of breast cancer among women at average and increased risk. *J Womens Health* (Larchmt). 2005;14:845-851.

STUDY: Perceived risk of colorectal cancer: sources of risk judgments

- ***Population studied:*** 648 adults 45-65 years old.
- ***Research question:*** How do people perceive their risk of colorectal cancer and why do they have those perceptions?
- ***Findings***

How Do People in the General Population Perceive Their Risk for Developing Colorectal Cancer?



- Factors that people believed would decrease their risk of colorectal cancer: diet, family history, and symptoms/general health.
- Factors that people believed would increase their risk of colorectal cancer: symptoms/general health, family history, smoking, and diet.

- ***Conclusion:*** People use both logic (analysis of risk factors) and previous experiences to judge their personal risk of cancer.
- ***Citation:*** Robb KA, Miles A, Wardle J. Perceived risk of colorectal cancer: sources of risk judgments. *Cancer Epidemiol Biomarkers Prev.* 2007;16:694-702.

The results of these three studies illustrate several important themes in cancer risk perception: people do not always accurately perceive their risk of developing cancer and these perceptions are influenced by a variety of factors other than logical analysis.

In a review article on cancer risk and communication (Klein and Stefanek, 2000), investigators describe some other factors that are related to risk perception, as outlined below. These factors are not confined to how people perceive their risk of developing cancer, but to other types of cancer risk including the risk of recurrence and risk associated with various treatments. Some of the factors described in this article apply to how we understand information in general. For more information on these findings, you can access their article freely on the internet at the following Web site: http://onlinelibrary.wiley.com/doi/10.3322/canjclin.57.3.147/pdf.

PSYCHOLOGICAL PROCESSES THAT UNDERLIE RISK PERCEPTION

Process	Examples and Discussion
Innumeracy People find it difficult to think about numeric information such as risk percentages and proportions. This is known as "innumeracy" in many of the published articles.	People have trouble with the following information: If a person's chance of disease is .0005, how many people out of 10,000 would get the disease? In one study, fewer than half the people got this answer correct. People also have difficulty converting proportions to percentages and vice versa. (If you are one of these people, see Chapter 6: Understanding Risk Information.) Some researchers have pointed out that schools do not focus on teaching this type of probability information, opting instead to focus on geometry and other areas of mathematics that are not as relevant to our daily lives. Regardless of the reason, innumeracy is considered an important impediment to understanding cancer risk.
Heuristics Heuristics are rules of thumb. We all use rules of thumb to make sense of information and these can be helpful or harmful depending on a variety of circumstances.	People tend to give priority to information that is accessible and readily available: If your sister told you something that she heard about cancer last week, you may rely on that instead of looking up the information on a National Cancer Institute Web site or asking your doctor. If your sister is right, everything is fine; if she is wrong, you may be influenced by misinformation. Another rule of thumb is to believe speakers who appear credible and disregard information from speakers who do not. This bias can lead us to make faulty judgments if the less credible speaker is correct.
Motivational factors The perception of cancer risk may also be influenced by motivational factors such as the wish to appear rational instead of emotional, the wish to appear informed, the tendency to compare oneself with others, the tendency to avoid loss, and the need to defend against the possibility of bad news.	People have a need to appear rational: When making important decisions, people often seek information that does not influence or impact their decisions (notably, this is also true for physicians). Social comparison is an important motivating factor: In several studies of young women who overestimated their breast cancer risk, social comparison information was the most effective type of information in helping them perceive their risks adequately and reduce cancer-related worry. Several studies have asked people to read short stories designed to provoke sadness, anger, or happiness. When people read sad stories, they tend to rate their own risk of cancer and other diseases too high, whereas when they read stories designed to provoke happiness or anger, they tend to rate their own risk of cancer lower than average.
Emotional influences Emotions have a major effect on risk perception.	These findings suggest that cancer studies designed to determine how people perceive cancer risk may need to take multiple measures over time in order to obtain accurate results (i.e., if people are sad on Monday, they may rate their risk of cancer higher than on another day when they are happier). Additionally, worry about cancer is associated with engaging in risk-reducing behaviors such as exercise and avoidance of/quitting smoking.

Information from Klein WM and Stefanek ME. Cancer risk elicitation and communication: lessons from the psychology of risk perception. *CA Cancer J Clin*. 2007;57(3):147-67.

Risk-Benefit Trade-Offs

For people who have not yet developed cancer, risk-benefit trade-offs may consist of weighing the risks of screening for cancer with potential benefits of detecting cancer early. Alternatively, the risk-benefit trade-offs may consist of weighing the risk of a preventive surgery with the benefit of avoiding cancer. People who have already been diagnosed with cancer may consider the risk-benefit trade-offs of various therapies. In this regard, knowing the risk of side effects can help people decide which cancer treatment to undergo. However, other major factors in the decisions are the potential benefit to be gained from treatment and the risk of cancer recurrence in the future. Treatments are not 100% effective and side effects are not 100% certain. Instead, individuals are faced with a likelihood of benefit weighed against a likelihood of risks.

One factor that can influence the risk-benefit trade-off is a person's health status. In individuals without cancer, health factors can influence the risks associated with screening tests. For instance, colonoscopy — a screening procedure for colorectal cancer — is generally a safe procedure but causes serious adverse events in 0.28% of individuals (American Society for Gastrointestinal Endoscopy, 2011). Risk factors for complications with this procedure include cardiovascular conditions, problems with blood clotting, and treatment with certain drugs. For individuals with cancer who are weighing the risk of treatment complications, other health conditions besides cancer can be important to consider. For example, people with heart disease may be at greater risk for cardiac side effects and thus may opt in favor of a cancer treatment that has a lower risk of affecting the heart.

Another factor that can influence the risk-benefit trade-off is the stage of cancer. For instance, someone with metastatic cancer may be more willing to put up with serious side effects than someone whose cancer is not likely to spread. Physicians may also be more likely to recommend aggressive treatment to those with metastatic cancer. This can be seen in prostate cancer where the disease is classified as low-risk, medium-risk, or high-risk based on its likelihood of invading other tissues (as determined by three different types of tests or analyses). Examples of research findings in this area are included in the following section on perceptions of cancer recurrence risk and in the subsequent section on risk perception in metastatic breast cancer patients.

Researchers at the University of Michigan Comprehensive Cancer Center are studying how patients make treatment decisions, how doctors make treatment recommendations, and how to improve the process for better patient outcomes. One of the important observations related to this program is that approximately 95% of women who are diagnosed with breast cancer at an early stage survive. Treatment for these cancers may have the potential to harm more than help women if it is too aggressive. The program promotes greater patient understanding and appreciation of treatment risks and benefits and a weighing of the options taking into account each individual's unique situation, including tumor, family history, lifestyle, and values. For more information on this program, you may want to visit the following Web site: www.mcancer.org/.

Perception of Cancer Recurrence Risk

Being diagnosed with cancer is an extremely stressful event that upends people's lives and causes anxiety, worry, and fear. Selecting a treatment while under such stress can be a daunting task. Although getting rid of the current cancer is clearly a primary goal, minimizing the risk of recurrence is also a consideration. Research has demonstrated that risk of recurrence can influence treatment selection. Given the importance of treatment selection, it seems fair to ask whether patients accurately perceive their risk of recurrence and how this influences treatment decision making. Many studies have examined these questions from various angles, using different research strategies. In this section, we consider some of the findings related to patient perception of risk. Most of the research in this area has focused on breast cancer patients, but a few studies have been conducted with other patients.

Perceptions Related to Risk of Recurrence

One consistent finding is that most patients with early-stage breast cancer do not perceive their risk of recurrence accurately. One study of 531 women with early-stage breast cancer found that only 17% accurately perceived their risk of recurrence at 6 months (Liu et al, 2010). In this study, patients who were nonwhite or who received radiation therapy were more likely to underestimate their risk, whereas patients with ductal carcinoma in situ, lower social support, or anxiety were more likely to overestimate their risk. Other research has found that women with ductal carcinoma in situ overestimate their risks of recurrence, which can cause distress and reduced quality of life. In a study of 181 women with a history of ductal carcinoma in situ, 32% perceived at least a moderate 5-year risk for recurrence; this can be compared to the actual 5- to- 10-year risk of recurrence of 5-8% (Ruddy et al, 2013). Lower levels of financial comfort and lower levels of education were associated with an overestimation of risk. Yet another study found that, for women with a history of breast cancer, greater worry, living in a rural area, and longer time since diagnosis were associated with more inaccurate risk of recurrence assessments (Kelly et al, 2013).

As noted previously research indicates that perceived risk of recurrence has an important influence on treatment decisions (Fisher et al, 2012). Although studies have repeatedly shown no differences in survival of women treated with mastectomy versus lumpectomy for early-stage breast cancer, the latter is associated with a higher likelihood of in-breast recurrence. In a study of 310 women, 44% of 88 patients less than 50 years of age and 41% of 222 patients 50 years of age or older chose mastectomy over breast conservation surgery, even though the latter was an option (Fisher et al, 2012). Women in both age groups cited lower recurrence risk and improved survival as the major reasons for their choices. Thus, in this study, it appears that the lower recurrence risk was highly important to women and they inaccurately perceived a difference in survival between the two options.

Given the availability of predictive genomic tests such as Oncotype DX® and MammaPrint® for some breast cancers, it is interesting to ask how much women are influenced by these results. A study of 77 early-stage breast cancer survivors examined how women weighed the findings of genomic tests versus standard clinical tests such as tumor size in determining risk perception (Defrank et al, 2012). Results showed that, when the information from the two tests conflicted, women gave more credence to the results of genomic tests. This study also found that perceived risk of recurrence heavily influenced the decision to undergo adjuvant chemotherapy.

Other research suggests that "health literacy," a measure of a person's familiarity with health-related concepts, predicts risk perceptions. That is, women with higher health literacy were more accurate in their estimates of perceived risk of cancer recurrence than were women with lower health literacy (Brewer et al, 2009). This study adds to a growing literature indicating that education and communication are important in helping patients to understand their risk of recurrence.

However, other research suggests that education and communication may not be enough to alter risk (mis)perception and its influence on treatment decisions. An article with an interesting title suggests that emotion may play a large role in risk perception: *Why a 6% risk of cancer doesn't always feel like 6%* (Zikmund-Fisher et al, 2010). These authors present evidence that emotion and the way that risk information is presented heavily influence risk perceptions. According to the author, these emotions may sway cancer decisions perhaps more than factual knowledge. They suggest, "that anyone discussing future risks with cancer survivors or their caregivers should specifically draw attention to important non-recurrence risks in order to appropriately balance these risks versus the vivid risks of cancer recurrence."

Relationship Between Risk Perceptions and Lifestyle Behaviors

Some research with lung cancer patients has evaluated the relationship between perceived risk of cancer recurrence and smoking behavior. In a group of 188 patients with newly-diagnosed lung cancer, those who perceived their risk of recurrence to be higher were the most likely to stop smoking (Hay et al, 2007). In this group, patients were fairly accurate in their estimates of risk, suggesting a difference between lung cancer patients and early-stage breast cancer patients. The authors of this study concluded that perceived risk of cancer recurrence may motivate people to quit smoking.

Similarly, colorectal cancer survivors may have fairly realistic risk perceptions and those perceptions may influence lifestyle behaviors. In a study of 80 men and women who survived colorectal cancer, perceptions related to risk of recurrence, anxiety, and worry were associated with higher intent to make healthy behavior changes (Mullens et al, 2004).

Taken together, these results suggest that some of the negative emotions associated with cancer survivorship may motivate behavior change. This worry or risk-related motivation may perhaps be beneficial in situations where lifestyle factors have been linked to cancer.

It is also important to determine whether there are differences in the accuracy of risk of recurrence perceptions in different types of cancer. Research from different studies raises the possibility that people more accurately gauge their risk when their risk is higher rather than lower; said another way, it may be difficult for people with a very low risk of recurrence (5-10% or even less) to believe the accuracy of such low risk numbers.

Historically, cancer has been a devastating diagnosis. Everyone knows someone who has died of cancer, which fuels its reputation as a deadly disease. Even if a person's risk of recurrence is only 8%, the idea of being one of the 8 of 100 people can be profoundly disturbing. This may be especially true if people believe they can prevent that situation by selecting a more intense therapy regimen. People may fear that next time the disease will be worse or treatment will be less effective. Although biomedical journals increasingly describe many forms of cancer as treatable chronic diseases, it may take time to change public opinion. It may simply be hard to imagine that such a potentially deadly disease that has taken friends or family can now, in some cases, be controlled. Education will likely be helpful in combating inaccurate risk perceptions but it may also be necessary to combat public opinion—a difficult task when some forms of cancer are highly treatable and others remain intractable.

Risk Perception in Individuals With Metastatic Cancer

Individuals with metastatic cancer (i.e., cancer that has spread away from its original location) may have different concerns than those with localized cancers and thus their risk perceptions may differ. A recent study by Smith and colleagues examined how people with metastatic breast cancer weigh the risks and benefits of treatment (Smith et al, 2014). This study, which was presented at the American Society of Clinical Oncology in 2012, asked people who had a history of metastatic breast cancer to read 14 different treatment scenarios that varied in terms of likelihood of benefit (defined as shrinkage of advanced cancer, responding to treatment), toxicity, and medication format. Participants were asked to choose between two treatment scenarios and to indicate whether or not they would undergo the treatment. Overall, results indicated that the likelihood of benefit was more important to people than toxicity—at least at the benefit and toxicity ranges presented in the study, which were chosen to be similar to those experienced with actual cancer drugs. Most of the 641 people who filled out the survey answered in ways that indicated that they would opt for a treatment with a 27% or 33% likelihood of benefit regardless of the side effect scenario presented (note that the benefit levels were given as fixed percentages in a written scenario and not as a range). The severity, duration, and type of toxicity did not have a large influence on the decision to undergo treatment under the conditions specified in the study. These results seem to indicate that women with metastatic breast cancer are highly influenced by the potential for treatment benefit.

Another study conducted by researchers in North Carolina examined treatment preferences and benefit-risk trade-offs among 115 women with metastatic breast cancer (McQuellon et al, 1995). Women were presented with hypothetical treatment scenarios in which toxicities and life expectancy durations were varied (1 week to 5 years); for each scenario, the chance of achieving the given life expectancy was set at 50%. Results showed that women were less likely to accept treatment as the toxicity potential increased. However, 15% of women indicated that they would opt for high-risk treatments that would only be expected to add 1 month of life. Nearly all women indicated that they would opt for treatment that might be highly toxic when the increase in life expectancy was 5 years. Like the Smith study described in the previous paragraph, these results also suggest that potential for benefit is extremely important to people with metastatic breast cancer, but the types and levels of toxicity presented in this study had a strong influence.

A study conducted by two British researchers examined risk-benefit trade-offs in 81 patients previously treated with chemotherapy for advanced non-small cell lung cancer (Silvestri et al, 1998). The patients were given three hypothetical scenarios describing a single patient with metastatic non-small cell lung cancer with an expected survival of 4 months without treatment. Results showed that the minimum survival benefit needed for patients to accept the toxicity of chemotherapy varied widely. Some indicated that they would accept chemotherapy for a survival benefit of 1 week, whereas others would not even elect to undergo chemotherapy for a survival benefit of 2 years. Additionally, 78% of patients (63 of 81) indicated that they would not choose to undergo chemotherapy for a survival benefit of 3 months unless it improved quality of life.

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Chapter 5: Understanding Numeric Risk Information

We all know that long hours spent out in the sun or in tanning salons increase our risk of developing skin cancer. Although most of us don't typically consider how much our risk is increased, we likely pay more attention to something that increases our risk of cancer by 100% than by 1%. That is, we know that higher numbers are worse or indicate greater risk. However, risk numbers can be expressed several different ways and can have vastly different interpretations depending on exactly what is being measured. Moreover, risk can be conveyed in verbal statements that do not include numbers.

In this chapter, we discuss some of the most common numeric methods of presenting risk information to patients and the public, as well as the methods of presenting information in cancer studies.

Absolute Versus Relative Risk

When considering cancer risk, it is helpful to understand the distinction between absolute risk and relative risk. Absolute risk refers to the likelihood of a certain event happening in a given period of time. A person's absolute risk of cancer is the likelihood that a person will develop cancer over a designated period of time. One of the most commonly specified time periods is a person's entire life—or the risk that a person will develop cancer during his or her lifetime. However, risk does not have to be specified as lifetime. We may be interested to know risk over a shorter period of time such as 5 years or 1 year, or between certain ages.

Absolute risk: the likelihood of a certain event happening in a given period of time, such as the likelihood that a person will develop cancer over a lifetime.

Relative risk refers to the likelihood of a certain event happening in one group compared to the likelihood of the same event happening in another group. The two groups differ on some important characteristic or behavior. For example, we may be interested in attempting to reduce our risk of cancer through regular exercise. You may hear statements such as regular exercise reduces the risk of cancer by 15%. This means that people who exercise regularly are 15% less likely to be diagnosed with cancer than those who don't.

Relative risk: the likelihood of a certain event happening in one group compared to another group, such as the likelihood of cancer in those who exercise versus those who don't.

Relative risk is also frequently used to express the increased likelihood of cancer caused by the presence of certain genetic mutations. For example, women with BRCA1 or BRCA2 mutations are approximately 5 times more likely to develop breast cancer than those without either of these mutations.

Let's consider how relative risk relates to absolute risk. Women without BRCA1 or BRCA2 mutations have a 12% lifetime risk of developing breast cancer. Women with BRCA1 or BRCA2 mutations have a 60% lifetime risk of developing breast cancer. The 12% and 60% are absolute risks because they refer to the likelihood of a certain event (developing breast cancer) over a period of time (lifetime). We can calculate the relative risk of developing breast cancer if a woman has a BRCA1 or BRCA2 mutation like this: 12% multiplied by what number equals 60%? Dividing 60 by 12 gives us 5, so we know that the risk of developing cancer differs by a factor of 5. Another way to say this is that women with BRCA1 or BRCA2 mutations are 5 times more likely to develop breast cancer than women without those mutations.

100 women without BRCA1 or BRCA2 mutations

12 will develop breast cancer in their lifetimes

12 out of 100 = 12%

100 women with BRCA1 or BRCA2 mutations

60 will develop breast cancer in their lifetimes

60 out of 100 = 60%

60% is how many times more than 12%?

60 divided by 12 = 5

Women with BRCA1 or BRCA2 mutations are 5 times more likely than women without those mutations to develop breast cancer over their entire lifetimes.

Another example indicates the dangers of confusing absolute and relative risk. For females, the lifetime risk of developing esophageal cancer is 1 in 435 or 0.23%. Let's say that the presence of a certain mutation increases your risk of developing esophageal cancer by 100%. Should you be alarmed? Typically, when we hear numbers of 100% or more associated with cancer risk, it can be disconcerting. However, in this case, a 100% increase in risk means a doubling of 1 in 435 to 2 in 435, or from 0.23% to 0.46%. A risk of 2 in 435 or 0.46% is still quite low, even though it represents a 100% increase over the risk of someone without the mutation.

As advocates, it is critical to be aware of the distinction between absolute and relative risk. Cancer studies that are picked up by the media may proclaim that some behavior, such as taking a certain drug or vitamin supplement, doubles the risk of cancer. If a person's risk for that cancer is 1 out of 500 (0.2%) to begin with, a doubling would raise it to 2 of 500 (0.4%)—still not very likely. People frequently misunderstand the relative risk numbers and become needlessly alarmed. An interesting article on the Breast Cancer Choices Web site discusses this problem: www.breastcancerchoices.org/rr.html. This is not to say that relative risk numbers are useless, but rather that it is important to understand them and put them into context by knowing the absolute risk numbers.

ABSOLUTE RISK VERSUS RELATIVE RISK

Type of Risk	Definition	Examples
Absolute	Risk that a person will develop cancer over a designated time period	• Risk of brain cancer in a person's lifetime • Risk of breast cancer in women >50 years of age • Risk of leukemia in children <12 years of age
Relative	Risk compared to a group that differs on a key factor (i.e., the risk factor)	• Risk of lung cancer in a group of smokers vs. non-smokers • Risk of prostate cancer in men <50 years of age vs. those 50 years or older • Risk of colon cancer in men vs. women

Expressing Risk Numbers

To understand how risk numbers are expressed, we need to travel back to fifth-grade math. Risk is usually given as a percentage or a proportion. When expressing absolute risk, a percentage refers to the number of people out of 100. For example, a 25% risk means 25 people out of 100. A 1.35% risk mean 1.35 people out of 100. Because you can't have 0.35 parts of a person, it is often helpful to get rid of the decimal. In this case, because you have 2 decimal places, you add 2 zeros to the bottom number (100) to get 135 out of 10,000.

When percentages are used to express relative risk, they refer to the percentage increase or decrease compared with some other group. As we discussed previously, a factor that doubles the likelihood of getting cancer is said to increase cancer risk by 100%.

Proportion is another way to express absolute risk. Proportion is essentially a fraction or some number of people out of a larger group such as 1 out of 2 or 6 out of 10. When using a proportion to express risk of disease, we usually specify 1 person as the top number of the fraction and then indicate how many people need to be included in order for 1 person to be diagnosed with cancer. For this reason, you may see numbers like 1 of 88 people or 1 of 225 people.

Proportions are not usually used to express relative risk except in cases where the fraction is simple such as 1/2 or 1/3. For example, you could say that men have half the risk of women of developing a certain type of cancer. It is also possible to say that a certain gene mutation increases the risk of cancer by 3/10, but saying 30% makes more sense to most people and thus percentages tend to be used more frequently than proportions for expressing comparisons.

Percentages can be converted into proportions and vice-versa. The following table shows some examples of converting percentages into fractions and vice-versa.

EXAMPLES OF ABSOLUTE RISK EXPRESSED AS PERCENTAGES AND PROPORTIONS

Risk as a percentage	What does it mean?	How to figure proportion from %	Risk as a proportion	What does it mean?	How to figure % from proportion
50% = 50/100	50 people out of 100	50/100 = 1/x Divide 100 by 50 to get 2	1/2	1 person out of 2	1/2 x 100 Divide 1 by 2 and multiply by 100 to get 50
1.27% = 127/100	1.27 people out of 100 Multiply each number by 100 to get rid of the decimal = 127 people out of 10,000	1.27/100 = 1/x Divide 100 by 1.27 to get 78.7, which rounds up to 79	1/79	1 person out of 79	1/79 x 100 Divide 1 by 79 and multiply by 100 to get 1.265, which rounds up to 1.27

How is Risk Portrayed in Cancer Studies?

When reported in cancer studies, risk can be portrayed as absolute or relative depending on the study design. Studies that examine absolute risk usually report the likelihood of an event happening over time as a proportion such as 1 person out of 35 studied develops cancer over a 10-year period. Many cancer studies examine relative risk by comparing one group to another. In such cases, risk can be presented as a percent increase in risk or the number of times risk is increased or decreased in the study group versus the control group, as we saw in the last section. However, in published studies, risk is often presented in terms of odds ratios or hazard ratios and confidence intervals. As advocates, it is important to be familiar with these numbers and what they mean, but it is not necessary to memorize the exact definitions or learn how to do the calculations. Many researchers do not even know this—they leave it to the statisticians who are experts in the area. Let's take a closer look at each of these methods.

Odds ratios

The odds ratio measures the association between exposure to some factor such as smoking and an outcome such as lung cancer. The odds ratio is usually abbreviated OR and is given as a single number. In general, the higher odds ratio, the stronger the association.

In cancer research, odds ratios are often used in a type of study design known as a case-control study that is conducted to determine whether a certain factor such as smoking, red meat, sunlight, or asbestos increases the risk of cancer. The group that exhibits the outcome of interest, such as cancer, is known as the case group. The group that does not exhibit the outcome of interest (i.e., no cancer) is known as the control group. The odds ratio expresses the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure. For example, researchers may be interested in comparing the odds of lung cancer (outcome) in smokers (exposure) compared to the odds of lung cancer (outcome) in non-smokers (absence of exposure).

The important thing to know about odds ratios is that they allow us to infer that the risk of the outcome (such as lung cancer) is higher or lower for people who are exposed to the variable (such as smoking). The other important thing to know about odds ratios is how to interpret the actual odds ratio numbers. Here are the rules for interpreting odds ratios:

- OR = 1 Exposure does not affect odds of outcome
- OR > 1 Exposure associated with higher odds of outcome
- OR < 1 Exposure associated with lower odds of outcome

For example, a case-control study comparing smokers and non-smokers with regard to the development of lung cancer may report an odds ratio of 30. This is usually interpreted as smokers are 30 times more likely to get lung cancer than non-smokers. In this example, smoking is the variable to which people have or have not been exposed and lung cancer is the outcome of interest.

Importantly, case-control studies do not allow us to conclude that one variable causes another, even if the odds ratio is high as it is with smoking and lung cancer. Odds ratios tell us only whether a variable and an outcome are associated with one another.

To learn more about odds ratios, you may want to consult the following articles, which are freely available on the internet:

- Szumilas M. Explaining odds ratios. *J Can Acad Child Adolesc Psychiatry*. 2010;19:227-9.
- Centers for Disease Control and Prevention. Cigarette smoking and lung cancer. Available at: www.cdc.gov/excite/classroom/smoking_q.pdf and www.cdc.gov/excite/classroom/smoking_a.pdf

Odds ratio: measures the association between an exposure and an outcome of interest; odds that an outcome will occur given exposure to the variable of interest compared to the odds of the outcome not occurring in the absence of exposure to the variable. Odds ratios are also used in observational studies to show association (not causation); for instance, they may be used to show how something is associated with an outcome at a certain point in time.

Hazard ratios

Hazard ratios are another way to express relative risk. A hazard ratio is a measure of how often a particular event happens in one group compared to how often it happens in another group. In cancer research studies, hazard ratios are often used for two types of analyses: (1) disease-free survival—how many people are still alive and disease free at a given time and (2) overall survival—how many people are still alive at a given time. Hazard ratios express the opposite of survival; that is, they express how many people experience a certain event, which is typically disease progression or death in cancer studies. However, hazard ratios are not limited to cancer studies, nor are they limited to the endpoints of disease-free and overall survival. Their interpretation must be considered in the context of the study.

Like odds ratios, hazard ratios are expressed as single numbers and their interpretation is as follows:

- HR = 1 No difference between groups in the frequency of a particular event (hazard)
- HR > 1 Exposure associated with higher odds of a particular event (hazard)
- HR < 1 Exposure associated with lower odds of a particular event (hazard)

An example of a study in which a hazard ratio may be generated is when you are testing disease progression with a new cancer drug (experimental group) against an established drug (control). If you obtain a hazard ratio of 0.3 at a given follow-up time, you know that patients in the experimental group were 0.3 times as likely to experience disease progression at a given time as those in the control group. This means that the experimental group was less likely than the control group to experience disease progression.

Hazard ratio: how often an event happens in one group compared to how often it happens in another group at a particular time.

To learn more about hazard ratios, you may want to consult the following articles, which are freely available on the internet:

- Blagoev KB, Wilkerson J, Fojo T. Hazard ratios in cancer clinical trials—a primer. *Nat Rev Clin Oncol.* 2012; 9(3):178-83.
- Spruance SL, Reid JE, Grace M, Samore M. Hazard ratio in clinical trials. *Antimicrob Agents Chemother*. 2004;48(8):2787-92.

Confidence intervals

In research studies, odds ratios and hazard ratios are reported along with confidence intervals around them, usually abbreviated CI. (Just a note that confidence intervals are not limited to odds ratios and hazard ratios—they can be used with other types of statistics.) The confidence interval is expressed as a range that tells you how precise the odds ratio or hazard ratio estimate is. Confidence intervals are therefore related to measures of the average treatment effect. They are not valid for establishing a range of possible outcomes or for generalizing from a population level estimate to an expected personal experience. Instead, they are linked to the data set.

In clinical studies, an odds ratio of 1 means that the study group had the same outcome as the control group. Therefore, the result is often considered statistically significant if the range of the confidence interval does not include the number 1. For example, a confidence interval range of 1.8–3.7 does not include 1 and neither does 0.27–0.79.

Examples of confidence intervals that do not include the number 1
(results with ranges that do not contain the number 1 are usually considered significant)
1.3–1.9
2.7 –8.8
12.7–29.3

Examples of confidence intervals that do include the number 1
(results with ranges that do contain the number 1 are usually considered not statistically significant)
0.75–1.3
0.4–2.8
0.95–1.07

Ultimately, the goal of odds ratios and hazard ratios is to be able to predict what happens in the larger population, including those people who were not studied. Thus, the values obtained are estimates and confidence intervals allow us to determine how "confident" we can be that our estimates are valid and do actually apply to the larger population. The level of confidence is expressed as a numeric percentage, most commonly 95% or 99%. A confidence interval of 95% allows us to be 95% certain that the true value of the odds ratio or hazard ratio in the population is within the interval range specified. A 99% confidence interval allows us to be even more certain.

Confidence interval: a measure of precision of the estimate. A range of values that has a specified probability of containing the rate or trend. The 95% and 99% confidence intervals are the most commonly used.

Even though odds ratios and hazard ratios, with associated confidence intervals, are commonly reported in published clinical studies, they are not perfect measures. Studies that include very large numbers of patients are more likely to result in statistically significant results, although the results may not be clinically significant. For example, a study of 100,000 patients randomized to either a placebo or a new drug may show statistically significant results (the confidence intervals do not cross 1), but only show an increase in survival of 1 week that may not be considered clinically important. Likewise, if a study does not include enough patients to show a statistically significant benefit between outcomes (this is termed "underpowered"), the study outcome may be misinterpreted as important. For example, a study recruits 20 patients who are randomized to either a placebo or a new drug treatment. At 6 months, 80% of the patients receiving the new drug are alive, whereas 60% of the patients receiving the placebo are alive. The results suggest that the new drug may be better, but not enough patients were recruited to show a statistically significant difference. For some criticisms on these measures and a more thorough discussion on how they should be used, you may want to consult the sources listed at the end of this chapter.

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Chapter 6: Communicating Cancer Risks

John was reading an article in the monthly health newsletter he received from his health insurance company. The article noted that a person could reduce his or her risk of getting colon cancer by 25% by making some lifestyle modifications such as eating less red meat. This led John to wonder about his own risk of colon cancer—was it high or low? Did he need to try to reduce it by 25%? Was 25% a big reduction or a small one?

This example illustrates the confusion that can be generated when using numbers to describe risk. However, sometimes numbers may be necessary. In this chapter, we describe several different methods of communicating cancer risk, including the use of verbal statements and graphic representations.

Verbal Versus Numeric Risk Statements

One prominent researcher in the area of patient perception of cancer risk and decision making suggests that risk communication should be tailored to the specific type of information that the patient wants or needs to receive (Zikmund-Fisher, 2013). That is, there are different formats in which a patient can receive information, some of which are more complex than others. Research suggests that simpler information formats can be used when patients need to determine whether their risk is more or less (or increased or decreased) compared to some other group. For instance, a person may want to quit smoking to decrease his or her risk of lung cancer. However, if the person is interested in how much his or her risk would decrease, more complex information presentation may be necessary.

Specifically, Dr. Zikmund-Fisher suggests that there are seven different types of risk communications. As shown in the following table, one of the main factors that distinguishes the type of risk communication is the degree of information precision. When a person asks how smoking will affect his or her risk of lung cancer—whether smoking will decrease his or her risk of cancer—the information being requested is not very precise. Thus, this information can be given in the form of verbal statements (increase or decrease/more or less), or statements of possibility such as high or low. Other times, patients want or need to receive precise numeric statements, or statements of probability or likelihood such as 50% or 1 in 2. For example, a person who has had a heart attack may want to know the likelihood of having another heart attack if he does undergo surgery versus if he does not undergo surgery. It should be noted that the types of risk communication are not specific to cancer, but rather are intended to apply to health in general.

PROPOSED TYPES OF RISK COMMUNICATIONS (ADAPTED FROM ZIKMUND-FISHER, 2013)

Type of Risk Communication	Explanation	Verbal or Numeric Expression of Risk (Determines precision)
Possibility	Something might or might not happen	Expression of risk is **verbal** (e.g., more than, less than, high, low)
Relative/comparative Possibility	Possibility compared to some other group (e.g., more, less or equally likely)	
Categorical possibility	Possibility of being in a given category (e.g., high risk, low risk)	
Relative probability	Increase or decrease in likelihood compared to some other group	Expression of risk is **numeric** (usually given as a % or proportion)
Absolute probability	Likelihood of something happening over a given period of time	
Comparative probability	Likelihood compared to another group	
Incremental probability	Change in probability	

According to Zikmund-Fisher, some examples of patient needs are as follows:
- Avoid surprise such as a rare treatment complication
- Motivate to act such as quitting cigarettes
- Make trade-off decisions such as radiation versus surgery
- Make magnitude-dependent decisions such as treatment that would reduce the risk of recurrence

In the first two examples, verbal information related to possibility may be most useful. For example, it may be more helpful to know that a treatment complication is extremely rare than to know that it occurs in a certain percentage of people. In the last two examples, numeric information may be useful. The bottom line of this strategy is that people communicating risk information, whether it is the writer of a health article or a healthcare provider communicating face-to-face with a patient, must determine the reason that the person needs the risk information. The best way to communicate this information can then be identified.

A group of experts have identified 10 steps to better risk communication, outlined in the following table (Fagerlin et al, 2011). For all of these steps, the goal is to make the information more understandable for patients.

TEN STEPS TO BETTER RISK COMMUNICATION

Step	Example
1. Use plain language to make written and verbal materials more understandable.	Write at an 8th grade level and use easy-to-read formats that contain a lot of white space.
2. Present data using absolute risks.	Say, "Your risk is 5%" not, "Your risk is 50% higher than the other group."
3. Present information in pictographs if you are going to include graphs.	When communicating 5%, include a graphic that has 100 squares with 5 of them shaded. Do not include a bar chart that shows a bar going up to 5%.
4. Present data using frequencies.	Say 5 out of 100 instead of 5%.
5. Use an incremental risk format to highlight how treatment changes risk from preexisting baseline levels.	Use a graph showing that risk of headache is 5 squares out of 100 without the treatment and 20 squares out of 100 with the treatment.
6. Be aware that the order in which risks and benefits are presented can affect risk perceptions.	Patients (and everyone else!) tend to be more influenced by information presented last—known as the recency effect. This can be minimized by using summary tables as described in #7.
7. Consider using summary tables that include all of the risks and benefits for each treatment option.	When presenting complex information that may have different risks and benefits, conclude with a summary table that lists the most relevant information to help jog a patient's memory.
8. Recognize that comparative risk information (e.g., what the average person's risk is) is persuasive and not just informative.	Presenting average risk and the patient's risk together may bias decision making. It may be better to present a patient's absolute risk by itself.
9. Consider presenting only the information that is most critical to the patients' decision making, even at the expense of completeness.	If a patient needs to make a decision between two treatments, provide the relevant information about those two treatments such as cancer-free survival with each, but avoid giving extraneous information such as expected cancer-free survival in people without cancer.
10. Repeatedly draw patients' attention to the time interval over which a risk occurs.	If risk information is given over 10 years, make sure patients pay attention to the 10 years and perhaps even give them 5-year or 15-year risk information for comparison.

Table adapted from Fagerlin A, Zikmund-Fisher, BJ, Ubel PA. Helping patients decide: ten steps to better risk communication. *J Natl Cancer Inst* 2011;103:1436–1443.

Research Results on Risk Communication to Patients

Research has examined how the format of risk information influences patient understanding. One study of 1619 women examined the graphic format used in Adjuvant! Online compared to a simpler format (Zikmund-Fisher et al, 2008). Study participants who viewed a 2-option graph more accurately stated the risk reduction from adjuvant chemotherapy than those who viewed the standard 4-option graph used in Adjuvant! Online. They also answered the risk question more quickly and preferred the 2-graph option.

Another study of 133 women with breast cancer examined understanding of risk based on a standard Oncotype DX® report format compared to other formats (Brewer et al, 2012). Women were most accurate in identifying whether a result was low, intermediate, or high risk with a continuum format (5% errors) and least accurate with the standard format (17% errors). However, women made errors 35% of the time when viewing a standard report format that showed high recurrence risk.

Yet another study examined whether presenting graphics in animated form helped improve patients' understanding (Zikmund-Fisher et al, 2012). More than 4000 people read scenarios of two hypothetical treatments for thyroid cancer. The treatments were equally effective but one had slightly fewer side effects than the other and thus was the better treatment option. Risk information was conveyed to participants in 1 of 10 different ways, including different types of animations or no animation. Results showed that none of the animations tested improved patient choice of the better treatment and most led to worse choices.

Overall, the research findings suggest that simplifying the format of risk information may help improve patient understanding. This is not to suggest that patients can't understand complex information, but rather recognizes that patients don't have experience looking at the various risk outcomes and that patients are likely under stress when attempting to evaluate these graphics and numbers.

Physician Perception of Risk

Another important consideration in cancer risk communication is physician perception. A 2004 study examined whether risk perception differs by physician specialty (Malek et al, 2004). Specifically, this study asked whether oncologists and surgeons differ in their recommendations of tamoxifen to their patients with stage I to IIIa breast cancer. Physician treatment recommendations were collected from 585 women who had previously been diagnosed with breast cancer. Results showed that physician perceptions of tamoxifen risks and benefits strongly predicted whether they recommended tamoxifen. However, oncologists were 2.5 times more likely to recommend tamoxifen than were surgeons. In making treatment recommendations, oncologists considered distant metastases and tolerance of tamoxifen side effects more important, and surgeons considered local recurrence and risk of cataracts more important.

A recent European study examined predictors of low screening rates for colorectal cancer among 940 patients in primary care settings (Fischer et al, 2013). Results showed that patients who were overweight or obese, born in regions other than Western Europe or North America, and male sex of the physician in charge were significant predictors of low screening rates among patients. The authors suggest that physician perceptions may have played a role in the reduced screening rates and that further research on physician perceptions is needed.

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Chapter 7: How Can Advocates Use This Information?

Risk information is useful to patients only if they understand it. All-too-often, risk information is presented in complex ways that may not optimally assist patients in decision making. Advocates can help in a number of different ways:

- Publicize or otherwise seek to make healthcare providers aware of research findings on how best to present information to patients so that they understand it.

  Research has repeatedly shown that simpler is better—less is more. In some cases, patients do not need to be given numeric information; verbal information may suffice. Two articles that have good information about these topics are listed below.

  Zikmund-Fisher BJ. The right tool is what they need, not what we have: a taxonomy of appropriate levels of precision in patient risk communication. Med Care Res Rev 2013 70: 37S. (The full paper cannot be accessed in its published form without payment, but the abstract is free at: www.ncbi.nlm.nih.gov/pubmed/22955699. A slide set describing these findings was presented by the author to the FDA and that is available at: www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/RiskCommunicationAdvisoryCommittee/UCM280630.pdf.)

  Fagerlin A, Zikmund-Fisher, BJ, Ubel PA. Helping patients decide: ten steps to better risk communication. *J Natl Cancer Inst* 2011;103:1436–1443. (The full paper is freely available at: http://jnci.oxfordjournals.org/content/early/2011/09/19/jnci.djr318.full.pdf+html.)
- Work with cancer organizations such as advocacy groups, governmental agencies, etc. to ensure that the risk information they communicate is presented in an understandable format.
- Develop workshops or Continuing Medical Education programs designed to help healthcare providers determine the best ways to communicate risk to their patients.
- Provide written materials for patients related to cancer risk information. This may include questions to ask, tables to fill in with information from healthcare providers (e.g., treatment options, toxicities, verbal or numeric risk information).

It is not only cancer patients who need to understand cancer risks, but also the general public. When results of studies are published, they often present cancer risk in relative terms that are then picked up by the media. For example, a certain type of vitamin may increase or decrease the risk of cancer by 100%. This high number may astound the public who may not realize the difference between relative risk and absolute risk. If the absolute risk were 1 in 500 (0.2%), a 100% increase in risk would be 2 in 500 (0.4%)—still a very low risk. Advocates may be able to influence this situation in a number of ways:

- Work to educate the public about the differences between absolute and relative risk.
- Provide information for the press regarding absolute and relative risk, such as differences between these two measures and providing both absolute and relative risk numbers when referring to study results.
- Urge cancer journals to include information about absolute risk in publications that examine relative risk.
- Work with organizations that have a strong presence on the internet to interpret the studies for the general public (e.g., American Cancer Society, National Breast Cancer Coalition [NBCC]).

Another group that needs to understand risk information consists of individuals who are at increased risk for developing cancer due to genetic abnormalities. In some cases, preventive surgery is available, whereas in other cases, frequent screenings are indicated. Helping people understand their options is critical and risk information is fundamental. Advocates may be able to help in the following ways:

- Work with governmental organizations and foundations related to cancer in general or the various cancer types (e.g., National Cancer Institute, Susan G. Komen®, Research Advocacy Network, Lynch Syndrome International) to ensure presentation of risk information in a way that individuals can understand.
- Develop written materials for use in healthcare offices that can be handed out to individuals at risk for cancers with a strong inherited component.

Organizations With Which Advocates May Want to Be Involved

Advocates can exert influence by participating in a variety of different programs, some of which are listed below. For a more thorough listing and description of these groups, you may want to consult the publication "Roadmaps to Advocacy" and advocate tutorials available through Research Advocacy Network (available to order at no charge at www.researchadvocacy.org.)

- National Cancer Institute study sections
- CDMRP Consumer Reviews (http://cdmrp.army.mil/cwg/default.shtml)
- Patient representative or advocacy committees/working groups in cancer cooperative groups
- ECOG-ACRIN Cancer Research Group: Eastern Cooperative Oncology Group (ECOG) and the American College of Radiology Imaging Network (ACRIN) (http://ecog-acrin.org/)
- Alliance for Clinical Trials in Oncology (www.allianceforclinicaltrialsinoncology.org/)
- NRG Oncology (www.nrgoncology.org/)
- SWOG: South Western Oncology Group (www.swog.org/)
- Children's Oncology Group (COG) (www.childrensoncologygroup.org/)
- Specialized Programs of Research Excellence (SPOREs) sponsored by the National Cancer Institute (http://spores.nci.nih.gov)
- Online forums and discussion boards

Acknowledgements

Why Was This Guide Developed?

As advocates try to work within the system to advance research it is important to understand the basic tenets of the science. By gaining a better understanding, advocates can identify and illustrate the issues and problemsolve to support solutions. The emerging science and issues in research involving biomarkers were the motivation for developing this manual. We hope that this information will be helpful to advocates and others interested in advancing the science and improving care for cancer patients.

About Research Advocacy Network

Research Advocacy Network is committed to improving patient care through research. Our goals are to get results of research studies (new treatments) to patients more quickly, to give those touched by the disease an opportunity to give back and to help the medical community improve the design of its research to be more attractive to potential participants. Because research holds the hope for improvements in treatment, diagnostics and prevention, we are dedicated to patient focused research. We believe dissemination of research results to the medical community and patients can have a major impact on clinical practice.

The Research Advocacy Network (RAN) is a not for profit (501 c 3 tax exempt) organization that was formed in 2003 to bring together participants in the research process with the focus on educating, supporting, and connecting patient advocates with the medical research community. While there are many organizations addressing the needs of patients with specific diseases, political advocacy, cancer education and fundraising, RAN focuses on advancing research through advocacy and providing the patient perspective to the research dialogue.

RAN works with advocates and organizations to effectively integrate advocates into research activities. Please learn more about us at our Web site at www.researchadvocacy.org or contact us about our work by e-mailing us at info@researchadvocacy.org or by phone 877-276-2187 or FAX at 888-466-8803.

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