Special Section
Multiple Primary Cancers

Introduction

In the past three decades, the development of screening tests that prevent and detect some cancers at an early, more treatable stage, and treatment advances have increased the 5-year relative survival rate for all cancers combined from 50% in 1975-1977 to 66% in 1996-2004. The National Cancer Institute (NCI) estimates that there are more than 11 million cancer survivors in the US, more than 3 times the number in 1970. As the survivor population grows, it is increasingly important to address the unique needs of cancer survivors for medical surveillance, continuity of care, and information about how their cancer and its treatment may affect their future health. In addition to concerns about cancer recurrence, survivors also worry about their risk of developing a new cancer.

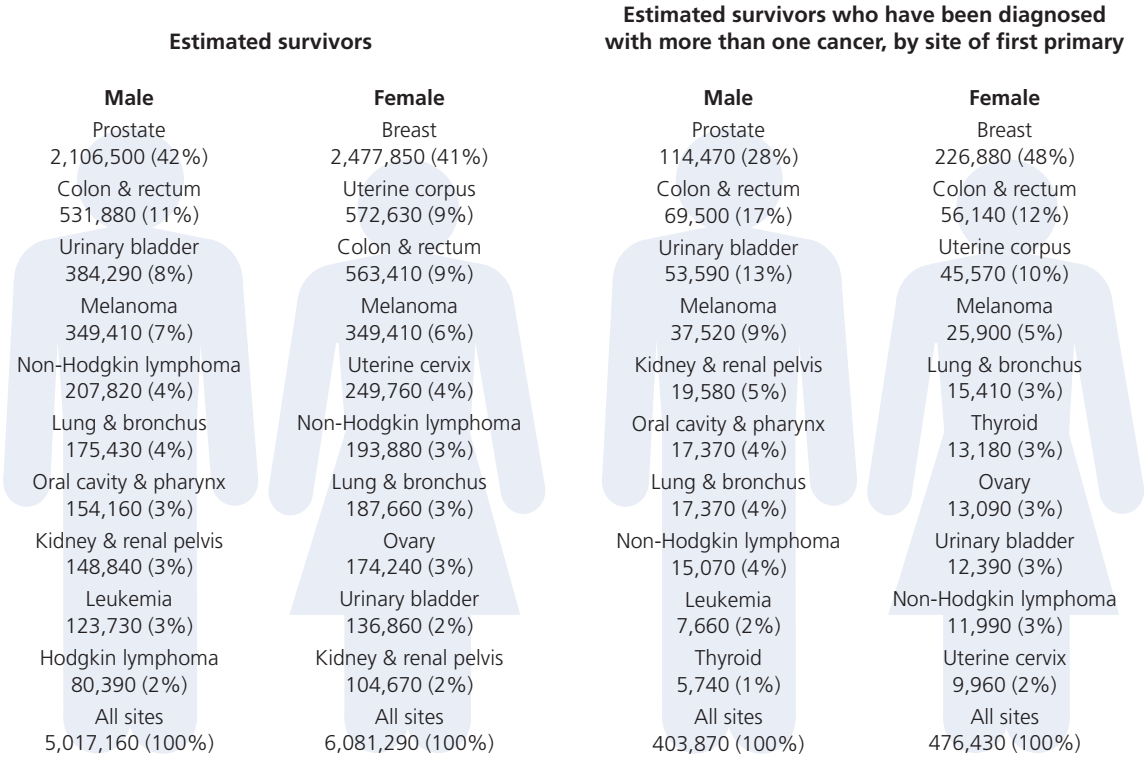
Approximately 880,300 of the 11 million cancer survivors living in the US as of January 1, 2005, had been diagnosed with more than one cancer. Most of these second or more cancers would be expected to occur even if cancer survivors had the same risk of cancer as the general population. The overall risk of cancer increases with age; for example, it is estimated that only 1% of 30-year-olds with no history of cancer will develop cancer in the next 10 years, compared to 18% of 70 year olds.[1] Although cancer survivors as a group have a small (14%) increased lifetime risk of developing new cancers compared with the general population, some subgroups of patients have a much higher risk. The risk of developing subsequent cancers varies by the type of first cancer diagnosed (referred to as the first primary site), age at first diagnosis, environmental exposures, genetic factors, treatment, and other factors. The purpose of this Special Section is to provide information about the burden and risks of multiple primary cancers, which will be useful to cancer survivors in understanding their risks and to health care providers in discussing risks of developing additional cancers with their patients.

This Special Section is organized into several broad topics. First, it provides background information about how clinicians and cancer registries define multiple primary cancers and descriptive statistics about the frequency and risk of subsequent cancers by primary site. It then describes the major factors that cause increased and decreased risk of multiple cancers, including family cancer syndromes and genetic susceptibility factors, shared-risk factors, and effects of treatment of a previous primary cancer. Next, it provides more detail on patterns of subsequent cancers for selected cancer sites (female breast cancer, colon and rectum, tobacco-related cancer, lymphomas, and melanoma) and childhood cancers. The final section describes American Cancer Society programs and resources for cancer survivors, including those who are at increased risk or have been diagnosed with more than one cancer.

How are multiple primaries defined?

- A cancer of a different site and histologic (microscopic composition of cells and/or tissue) type than the original cancer is considered a separate primary.
- Cancers of different histologic types in the same site are considered separate primaries regardless of whether they are diagnosed at the same or different times.
- A new cancer of the same site or with the same histology as an earlier one is considered the same primary cancer if diagnosed within 2 months or a separate primary cancer if diagnosed after 2 months, unless the medical record specifically states that it is recurrent or metastatic disease.
- If an organ is paired, each member of the pair is generally considered to be a separate site.
- Important exceptions to these general rules include most histological types of cancer in the prostate and urinary bladder, for which multiple tumors are reported as a single primary with the date of the first invasive lesion.
- A different set of rules is used to determine multiple primaries of the lymphatic and hematopoeitic (the production of blood cells) systems.

Figure 1. Estimated Number of Cancer Survivors* Alive as of January 1, 2005, and the Number Diagnosed with More than One Primary Site by Site of First Primary



* Rounded to the nearest 10.

Source: Angela Mariotto, Statistics, Research, and Evaluations Branch, Surveillance, Epidemiology, and End Results (SEER) Program, 17 SEER Registries, 1973-2005, Division of Cancer Control and Population Sciences, National Cancer Institute, 2008.

What Distinguishes a Recurrence from a Second Primary Cancer?

When a tumor is determined to be cancer, this indicates that cells within the tumor have developed the ability to invade into surrounding tissues and to move to remote sites (metastasize) where they can grow and invade. Even after treatment of the original cancer appears to have been effective, cancer cells may persist in the body and eventually grow to the point where they are detected either at or near the site of the original cancer or at a remote site. When this occurs, it is called a recurrence or a metastasis. By definition, a second (or multiple) primary cancer is the occurrence of a new cancer that is biologically distinct from the original primary cancer.[2] The determination of whether a new cancer is a separate primary or a recurrence or a metastasis from the original cancer is important clinically because it influences staging procedures, prognosis, and treatment. This determination usually involves a combination of pathological, clinical and, in some cases, additional laboratory studies. The distinction is easy when pathological information shows that the cancers being compared have different histological features that show that they have originated from distinct types of cells. Clinicians may also use information about typical patterns of recurrence and common sites of metastases for the first cancer. When the answer is not clear cut, molecular and cellular tools may be used to analyze the DNA of cells from the original and the new tumor to determine if they have a common origin, similar to taking a molecular fingerprint of the cancer. Tumor registries rely on the information in the medical record to determine whether a cancer is a recurrence or metastasis of a previously treated cancer, or a new cancer. In addition, cancer registries use coding rules to count multiple primary cancers in a consistent way. The coding rules consider the cancer site of origin, date of diagnosis, his-

Measures of risk for a subsequent cancer diagnosis among cancer survivors

Observed-to-Expected Ratio (O/E)

The observed number of cancers in a population of cancer survivors divided by the number of cancers expected. The number of cancers expected is calculated using cancer rates from the general population and person-years-at-risk (PYAR) of the survivor population under study. PYAR is counted from the date 2 months after the diagnosis of the first cancer (to exclude multiple primaries diagnosed at the same time) until the date of last known vital status or death, and allocated by age, sex, race, and calendar year. All second and later (third, fourth, etc.) cancer diagnoses are included.

Estimated absolute risk (EAR) per 10,000 PYAR

The EAR is calculated by subtracting the expected number of cancer cases from the observed number, dividing by the PYAR, and multiplying by 10,000 [((O-E)/PYAR) x 10,000]. The EAR represents the number of excess cancers per 10,000 PYAR (for example, a population of 10,000 cancer survivors followed for 1 year or 1,000 cancer survivors followed 10 years).

tology, behavior (i.e. in situ or malignant), and laterality of paired organs. Multiple primary cancers can either be diagnosed at the same time (synchronous) or at different times (metachronous); coding rules exclude cancers diagnosed within two months of the primary cancer, which are considered to be synchronous cancers, from the multiple primary counts. The coding rules used in this article are those used by the Surveillance, Epidemiology, and End Results (SEER) registries.[3]

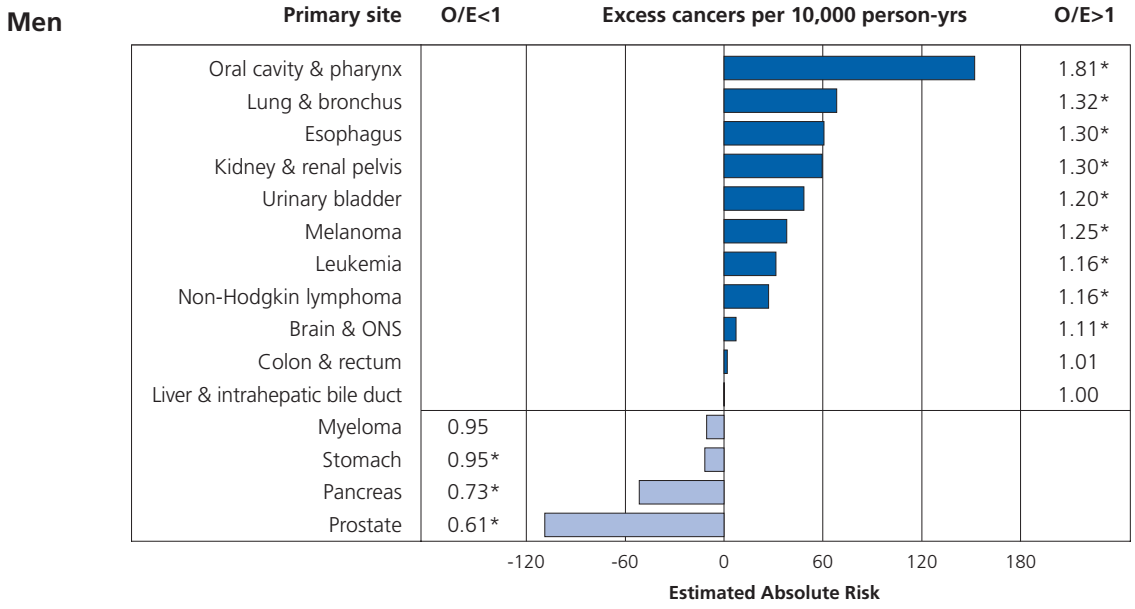
Population-based cancer registries are an important resource for studying multiple primary cancers. Registries collect information about each cancer patient in such a way that subsequent primary cancers diagnosed in the same person can be identified. The earliest studies of multiple primaries were done by cancer registries in Connecticut and Denmark.[4] More recently, the SEER Program published a monograph on new malignancies among cancer survivors based on data from the 9 original SEER registries during the 28-year period 1973-2000. The SEER Monograph, with data updated to 2005 (using SEER*Stat software version 6.4.4), is the primary resource for statistics used in this report and will be referred to throughout as the SEER Multiple Primary Study; the monograph can be accessed at http://seer.cancer.gov/publications.[5] The categories of primary and secondary cancer sites are provided in Appendix 2.A and 2.B of the monograph. In some cases, the categories reported for primary and secondary sites differ; for example, the category "acute myeloid leukemia" is used for primary sites and "acute non-lymphocytic leukemia," which includes acute myeloid leukemia and several other categories, is used for secondary sites. More information on the methods used and limitations of the study are provided in the Sources of Statistics section, from pages 17-19.

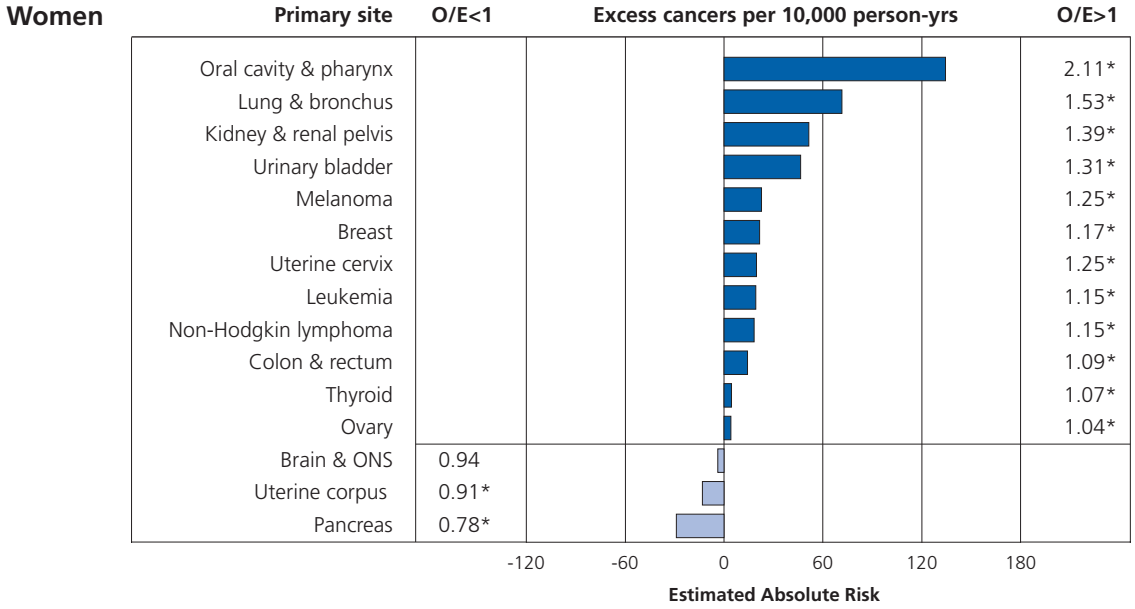
How Common Are Multiple Primary Cancers?

An estimated 880,300 cancer survivors who have been diagnosed with more than one cancer were living in the US as of January 1, 2005.[6] Among men who have been diagnosed with more than one cancer, the 10 most common primary sites are prostate, colon and rectum, urinary bladder, melanoma, kidney and renal pelvis, oral cavity and pharynx, lung and bronchus, non-Hodgkin lymphoma, leukemia, and thyroid (Figure 1). Among women who have been diagnosed with more than one cancer, the 10 most common primary sites are breast, colon and rectum, uterine corpus, melanoma, lung and bronchus, thyroid, ovary, urinary bladder, non-Hodgkin lymphoma, and uterine cervix (Figure 1). These rankings generally reflect high incidence and survival rates for the first primary cancer rather than unusually high risks for a subsequent cancer. For example, the large number of prostate cancer survivors who have been diagnosed with a multiple cancer reflects the fact that prostate cancer is the most commonly diagnosed cancer in men and has a 5-year relative survival rate of more than 99%, not that prostate cancer survivors have an increased risk of developing additional cancers. (See "What causes decreased risk of developing another cancer?" on page 30.)

The Observed-to-Expected Ratios (O/Es) and Estimated Absolute Risks (EARs) for subsequent cancers for the 15 most common primary cancer sites in men and women are shown in Figure 2. For both men and women, the highest O/Es and EARs are observed for cancers related to tobacco, including cancer of the oral cavity and pharynx, lung and bronchus, esophagus (men only), kidney and renal pelvis, and urinary bladder. Among men, primary sites associated with modest increased risks of subsequent cancer include melanoma, leukemia,

Figure 2. Estimated Absolute Risk (EAR) per 10,000 Person-Years and Observed-to-Expected Ratios (O/E) for Subsequent Cancers by Primary Site, Men and Women Ages 20 and Older, 1973-2005





Source: Surveillance, Epidemiology, and End Results (SEER) Program, 17 SEER Registries, 1973-2005, Division of Cancer Control and Population Sciences, National Cancer Institute, 2008.

Note: Top 15 sites are based on Jemal A, Thun MJ, Ries LAG, et al. Annual report to the nation on the status of cancer, 1975-2005, featuring trends in lung cancer, tobacco use, and tobacco control. *J Natl Cancer Institute* 2008;100(23):1672-1694.

Table 1. Observed-to-Expected Ratio and Estimated Absolute Risk of Developing Subsequent Primary Cancer by Age at Initial Cancer Diagnosis, SEER 1973-2005

Age at initial diagnosis	Male and female			Male			Female		
	Observed	O/E	EAR	Observed	O/E	EAR	Observed	O/E	EAR
All Ages	**258,997**	**1.14***	**21**	**140,888**	**1.12***	**22**	**118,109**	**1.17***	**21**
0-17	585	5.63*	17	266	5.69*	15	319	5.59*	19
18-29	2,171	2.41*	21	880	2.83*	21	1,291	2.19*	20
30-39	7,394	2.00*	33	2,315	2.22*	34	5,079	1.92*	33
40-49	20,501	1.51*	36	6,958	1.68*	48	13,543	1.44*	30
50-59	48,737	1.23*	29	23,097	1.28*	40	25,640	1.19*	22
60-69	85,461	1.12*	22	49,908	1.10*	22	35,553	1.14*	22
70-79	72,119	1.03*	8	45,015	1.02*	5	27,104	1.06*	12
80+	22,029	0.95*	-11	12,449	0.95*	-14	9,580	0.96*	-9

Note: Excludes the first 2 months after initial cancer diagnosis. Subsequent cancers exlcude non-melanoma skin and subsequent prostate cancers following an initial prostate cancer.

O/E = observed-to-expected ratio; EAR = excess absoute risk per 10,000 person years at risk (PYAR).

* $p<0.05$

and non-Hodgkin lymphoma; sites with no significant increase or decrease in risk include colon and rectum, liver and intrahepatic bile duct, and myeloma; and those with significantly decreased risk include stomach, pancreas, and prostate cancer. Among women, primary sites with modest increased risks include melanoma, breast, uterine cervix, leukemia, non-Hodgkin lymphoma, colon and rectum, thyroid, and ovary. Women who have had a primary brain cancer do not have significantly increased or decreased risk, and those who have a history of uterine cancer (including uterus not otherwise specified) or pancreatic cancer have a significantly decreased risk of subsequent cancer. Reasons that risk for second or more cancers differ by primary site are discussed below.

In addition to primary site, age at initial diagnosis is strongly associated with relative risk of developing a subsequent cancer (Table 1). Individuals diagnosed with cancer at ages 0 to 17 years have a substantially increased risk of developing subsequent cancers (O/E=5.63), with O/E ratios declining for patients diagnosed with their first cancer in each subsequent age interval (Table 1). Elevated O/Es for subsequent cancers among individuals diagnosed with cancer at younger ages are primarily related to genetic susceptibility and effects of radiation and chemotherapy treatment. Although the O/Es for subsequent cancers are highest for those diagnosed at ages 0 to 17 years, the absolute risks are not. The EAR for male and female patients diagnosed under age 18, 17 per 10,000 PYAR, is considerably lower than the EARs for middle-aged adults, which peak among men and women diagnosed at age 40 to 49 years (EAR = 36 per 10,000 PYAR) (Table 1). Persons diagnosed at age 80 and older have a significantly decreased O/E of subsequent cancer, likely reflecting in part underreporting of second cancers among elderly patients.

What Causes Excess Risk of Developing Another Cancer?

Cancers arise through a multistage process involving initiation, promotion, malignant transformation, and tumor progression. The critical initiating events often involve damage to DNA (the genetic material of the cell) that is not repaired before the cell divides, resulting in heritable mutations (permanent changes in the DNA) that are passed on to daughter cells. Mutations in critical areas of genes that regulate cell growth, cell death, or DNA repair may result in the selective growth of damaged cell lines and accumulation of further genetic damage. Factors that increase cell turnover, such as some hormones, can increase the proliferation of cells and the likelihood of malignant transformation even if they are not themselves mutagenic. In general, many mistakes in the DNA must accumulate for a cancer to develop. Factors associated with increased risk of developing more than one primary cancer have been grouped into three broad categories: familial cancer syndromes and other genetic susceptibility factors, common exposures (e.g. tobacco), and carcinogenic effects of cancer treatment. [7,8]

Familial Cancer Syndromes and Genetic Susceptibility Factors

About 1-2% of all cancers are associated with hereditary cancer syndromes; these syndromes are associated with very high lifetime probabilities of developing certain cancers.[7] Individuals with hereditary cancer syndromes have a heritable mutation in every cell, which may have been inherited from a parent or arisen early in development. Even in people with inherited syndromes, the development of cancer still depends on acquiring additional mutations. Many of these syndromes are autosomal dominant, which means there is a 50% chance that someone carrying the gene will pass it to their child. Retinoblastoma, a rare childhood cancer in the retina of the eye, is an example of an autosomal dominant hereditary cancer that is associated with a specific gene mutation in about 35% of all cases. Children born with this mutation have a very high probability of developing one or more retinoblastomas, as well as several other cancers, and are more susceptible to the adverse effects of radiation.[9]

Additional hereditary syndromes are associated with increased risk of developing multiple primary cancers.[9] Familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC) are two genetic syndromes that confer a high risk of colorectal cancer at an early age and at multiple sites within the colon and rectum. (See section on colon and rectal cancer on page 32.) Individuals with HNPCC are also predisposed to endometrial and ovarian cancers. Inherited mutations in the cancer susceptibility genes BRCA1 and BRCA2 are associated with early-onset breast and ovarian cancers and increased risk of second primaries of the breast, ovary, and other sites. (See section on breast cancer on page 30.) Heritable cancer syndromes should be suspected when several generations of a family are diagnosed with certain cancers at a relatively young age, or when several individuals in a family develop multiple primary cancers. When a heritable cancer syndrome is suspected, genetic counseling should be discussed because this may identify mutations in known cancer susceptibility genes.

Shared Risk Factors

Tobacco and alcohol use

Individuals may be at increased risk of developing multiple primary cancers due to exposure to risk factors that are associated with several cancers. As noted previously, individuals with tobacco-related cancer have very high O/Es for developing additional tobacco-related cancers. Tobacco smoke contains numerous carcinogens and prolonged exposure may result in a phenomenon called "field cancerization" in which there are multiple patches of transformed cells in the respiratory and urinary tract, some of which evolve to second (or more) cancers. Alcohol consumption has been associated with increased risk of a number of cancers, including oral cavity and pharynx, esophagus, liver, colon, larynx, and female breast. For some cancers, the risks associated with excessive alcohol consumption and tobacco use are much higher than for either exposure alone. It is estimated that alcohol consumption combined with tobacco use account for 75-85% of cancers of the oral cavity, pharynx, larynx, and esophagus in the US.[9]

Hormonal factors

Individuals may be at increased risk of developing multiple primary cancers due to hormonal factors that are associated with several cancers. Hormonal factors play an important role in the development of female breast cancer and several cancers of the female reproductive system. Studies of multiple primary cancers have found similar increases in relative risks for breast, ovarian, and uterine corpus cancers.[7, 9] This may result from common hormonal risk factors related to menstrual and pregnancy history and use of hormonal medications, as well as genetic susceptibility factors that increase risk for several cancers.

Immune deficiency and infection

Immunodeficiency syndromes, either acquired or inherited, are associated with an increased risk of non-Hodgkin lymphoma and some other cancers. Patients receiving immunosuppressive therapy after kidney transplants are at increased risk of non-Hodgkin lymphoma, Kaposi sarcoma, and squamous cell cancer on sun-exposed areas of their skin.[7] Suppression of the immune system may predispose a patient to other forms of skin cancer, including malignant melanoma. Patients with human immunodeficiency virus (HIV)-related immunodeficiency are at increased risk of non-Hodgkin lymphoma, Kaposi sarcoma, and cervical and anal cancer. Although case reports document multiple cancers in HIV-infected individuals, the relative risk for multiple primary tumors in patients with HIV-related immunodeficiency is unknown.

Human papillomavirus (HPV) infections are the main cause of cancer of the uterine cervix and have been implicated in other cancers of the anogenital tract (vulva, vagina, perineum, anus, and penis) for which there is evidence for mutually increased risk. There is growing

evidence to support a causal role for HPV, especially HPV-16, in oropharyngeal cancers.[10] HPV infections are relatively more aggressive and persistent in individuals with compromised immune systems.[7]

Effects of treatment of a previous primary cancer

Some of the treatments for cancer can damage normal cells and result in short-term and long-term side effects, including an increased risk of subsequent cancer years or decades later. The benefits of treatment of the first cancer are large compared to the risks of developing a second cancer.[11] The second cancers associated with radiation therapy include acute leukemia, chronic myelogenous leukemia, breast, lung, thyroid, and non-melanoma skin cancers.[12] Second cancers of the bone and connective (soft) tissues occur within or adjacent to the irradiated area among patients treated with high-dose radiation. Dose and type of radiation, the intrinsic susceptibility of exposed tissues, and patient characteristics influence the risk for radiation-associated cancers. The risk is generally higher when developing tissue is exposed at a young age. Improvement in radiotherapy techniques over time has allowed the damage to normal tissue to be minimized while delivering an effective dose to the cancer. Both radiotherapy and chemotherapy can cause treatment-related leukemia (most commonly acute non-lymphocytic leukemia). Chemotherapy drugs associated with increased risk of acute myeloid leukemia include some alkylating agents, topoisomerase II inhibitors, and anthracyclines. The carcinogenic potential of some chemotherapeutic drugs may be enhanced when administered in conjunction with ionizing radiation. Research has resulted in the development of chemotherapy agents that are equally or more effective in treating cancer while having less short-term and long-term toxicity to patients, including lower risk of second cancers.[13]

What Causes Decreased Risk of Developing Another Cancer?

Adult patients diagnosed with cancers that have low 5-year survival rates, such as pancreatic cancer, appear to be at decreased risk for second cancers. This may result in part from the exclusion of other cancers diagnosed within the first two months of the first, short interval of follow-up, and lack of differentiation of metastatic lesions from new primary tumors in terminally ill patients. Decreased risks for some cancers may be influenced by treatment and coding rules; this typically applies primarily to subsequent cancers of the same site. When a cancer is treated by removing an organ, the patient is no longer at risk for second tumors of that site. For example, many women with cancer of the uterine corpus are treated with hysterectomy and thus are not at risk for subsequent cancer of the uterine cervix or corpus. Some men with prostate cancer have their prostate surgically removed; in addition, coding rules specify that when second or more prostate cancers of the most common histological type (adenocarcinomas) are detected they are not considered a separate primary. When overall risk of subsequent cancer is thought to be influenced by treatment or coding rules for cancers of the same primary site, it is useful to examine the O/E ratio for cancers excluding the primary site. For the cancers mentioned above, the O/E calculated before and after excluding cancers of the same primary site goes from 0.91* to 0.96 for uterine corpus and 0.61* to 0.91* for prostate cancer. In contrast, the decreased risk of subsequent cancers after stomach cancer does not change after exclusion of the primary site (O/E in men and women combined changes from 0.91* to 0.92*); this may in part reflect the uniqueness of the primary risk factor for this cancer (*Helicobacter pylori* infection), which is not strongly associated with any other cancer. In addition, reduced rates of subsequent cancer may result from caloric restriction after stomach cancer treatment; reduced cancer mortality rates have been observed in long-term follow-up of patients with gastric bypass surgery.[14]

Multiple Primary Cancers Associated with Selected Primary Sites

Female breast cancer

Invasive breast cancer is the most frequently diagnosed non-skin cancer among women in the US and has a 5-year relative survival rate of 89%. The SEER multiple primary study found an O/E of 1.17 for all subsequent cancers among women diagnosed with a first primary breast cancer during 1973-2005 (Table 2).[15] New primary cancers of the breast account for nearly 40% of all cancers diagnosed among female breast cancer survivors, followed by cancer of the lung, uterine corpus, ovary, and acute non-lymphocytic leukemia. There is a strong relationship between younger age at diagnosis of the primary breast cancer and risk of a subsequent cancer (Table 2). Women diagnosed with early-onset breast cancer (age < 40) had almost a 3-fold increased risk of any subsequent cancer, with a 4.5-fold increased risk of subsequent breast cancer. In contrast, women diagnosed at age 70 and older had no excess risk of any subsequent cancer, and only a small (1.2-fold) increased risk of subsequent breast cancer. Genetic

Table 2. Observed-to-Expected Ratio for Developing Subsequent Primary Cancer after Female Breast Cancer by Age at Diagnosis of First Primary, SEER 1973-2005

Subsequent site	Birth to 39 (N=27,633)	40 to 49 (N=70,941)	50-69 (N=180,355)	70 and older (N=120,028)	All ages (N=398,957)	Observed number	Expected number	EAR
Breast	4.54*	1.98*	1.42*	1.20*	1.55*	18,523	11,932	19.64
Lung & bronchus	1.79*	1.24*	0.99	0.77*	0.96*	5,478	5,684	-0.61
Uterine corpus	1.77*	1.25*	1.32*	1.65*	1.40*	3,552	2,538	3.02
Ovary	4.67*	1.82*	1.16*	0.98	1.29*	1,815	1,408	1.21
ANLL	6.33*	3.31*	1.89*	1.03	1.74*	616	354	0.78
All subsequent cancers†	2.87*	1.49*	1.15*	0.99	1.17*	48,934	41,689	21.59

Note: Excludes the first 2 months after initial cancer diagnosis. Site definitions are based on Appendix 2a and 2b from Curtis RE, Freeman DM, Ron E, et al., (eds.) *New malignancies among cancer survivors: SEER cancer registries, 1973-2000*. Bethesda, MD: National Cancer Institute, NIH Publ. No. 05-5302; 2006.

EAR = excess absoute risk per 10,000 person years at risk (PYAR); ANLL = acute non-lymphocytic leukemia.

* $p<0.05$

† All subsequent cancers excludes non-melanoma skin cancer.

predisposition, notably mutations in BRCA1 and BRCA 2 genes, contribute to the excess risk of subsequent cancer among women with early-onset breast cancer. [7]

In addition to genetic predisposition, breast cancer survivors may be at increased risk of developing subsequent cancers of the breast and ovary associated with hormonal and reproductive risk factors, such as nulliparity (not having a child) and a long menstrual history (menstrual periods that start early and/or end late in life), as well as the adverse effects of treatment.[16] Patients receiving tamoxifen therapy for estrogen receptor positive breast cancer have a substantially decreased risk of recurrence and of developing a second primary breast cancer, but have an increased risk of developing cancer of the uterus.[16] The increased risk of acute non-lymphocytic leukemia (ANLL) among breast cancer survivors is thought to be related to some chemotherapy treatments, with radiation possibly adding to the risk.

Although the overall risk of lung cancer is lower for breast cancer survivors than the general population, an elevated O/E has been observed for women treated with radiotherapy after mastectomy.[5] While no significant excess risk has been reported among women receiving lower-dose radiation treatment after lumpectomy, women receiving this therapy may not have been followed long enough to detect such a risk if it was present. Radiation treatment may also be related to increased risk of several less common cancers among breast cancer survivors, including esophagus, bone, and soft tissue. Other relatively uncommon cancers that occur more frequently in breast cancer survivors are malignant melanoma, thyroid cancer, and salivary gland cancer. In contrast to some studies, the SEER study did not find significantly increased risk for colon cancer among breast cancer survivors.[15]

Recommendations exist for identification of women with primary breast cancer who have hereditary syndromes that increase the risk of developing multiple primaries. Women with predisposing mutations that increase the risk of breast and ovarian cancer may choose to undergo prophylactic bilateral mastectomy (removal of both breasts) or contralateral prophylactic mastectomy (removal of unaffected breast) after diagnosis of a primary breast cancer. Removal of the ovaries and fallopian tubes may also be considered because this reduces risk of subsequent invasive breast cancer by 50% and nearly eliminates the risk of ovarian cancer.[17] Both the American Society for Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) have published guidelines for follow-up of women after treatment for breast cancer.[18, 19] These guidelines recommend that all women who have had a diagnosis of breast cancer undergo regular physician visits, including history and physical examination and annual diagnostic mammography. Recent American Cancer Society guidelines recommend magnetic resonance imaging (MRI) in addition to screening mammography for women who have a high lifetime risk of breast cancer, including those with BRCA1 and BRCA2 mutations.[20] MRI is not recommended for women with a personal history of breast cancer, whose absolute lifetime risk of subsequent breast cancer is estimated to be 10%, because there is little data to support the benefits.[20]

Table 3. Observed-to-Expected Ratio for Developing Subsequent Primary Cancer after Cancer of the Colon, Rectum, and Rectosigmoid Junction by Age at Diagnosis of First Primary, SEER 1973-2005

Primary colon cancer

Subsequent site	Birth to 39 (N=4,614)	40 to 59 (N=41,397)	60-69 (N=54,664)	70 and older (N=112,500)	All ages (N=213,175)	Observed number	Expected number	EAR
Colon	12.46*	2.42*	1.67*	1.31*	1.57*	4,487	2,867	12.56
Rectum & rectosigmoid junction	12.24*	2.05*	1.23*	1.17*	1.36*	1,272	937	2.60
Uterine corpus	7.10*	1.54*	1.04	1.12	1.23*	697	567	1.01
Ovary	4.26*	1.42*	1.09	0.76*	1.01	340	338	0.01
ANLL	3.17	0.53*	1.10	1.02	0.99	238	241	-0.02
All subsequent cancers†	2.77*	1.22*	1.06*	1.00	1.06*	27,344	25,752	12.34

Primary cancer of the rectum or rectosigmoid junction

Subsequent site	Birth to 39 (N=2,361)	40 to 59 (N=23,731)	60-69 (N=26,210)	70 and older (N=39,380)	All ages (N=91,682)	Observed number	Expected number	EAR
Colon	7.45*	2.05*	1.40*	1.28*	1.45*	1,621	1,115	9.13
Rectum & rectosigmoid junction	7.57*	1.09	0.59*	0.92	0.86*	335	390	-1.00
Uterine corpus	4.28*	1.27*	1.06	0.84	1.07	227	213	0.26
Ovary	–	0.87	0.86	0.54*	0.72*	88	122	-0.61
ANLL	5.09	0.86	0.87	1.09	0.99	96	97	-0.02
All subsequent cancers†	2.14*	1.10*	0.98	0.94*	0.99	10,591	10,661	-1.27

Note: Excludes the first 2 months after initial diagnosis. Site definitions are based on Appendix 2a and 2b from Curtis RE, Freeman DM, Ron E, et al., (eds.) *New malignancies among cancer survivors: SEER cancer registries, 1973-2000*. Bethesda, MD: National Cancer Institute, NIH Publ. No. 05-5302; 2006.

EAR = excess absoute risk per 10,000 person years at risk (PYAR); ANLL = acute non-lymphocytic leukemia.

* p<0.05

† All subsequent cancers excludes non-melanoma skin cancer.

Colon and rectum

Cancers of the colon and rectum are the third most common cancer in men and women in the US, with a 5-year relative survival rate of 64%. The SEER multiple primary study found that most common second cancers among colon cancer survivors are new cancers of the colon and rectum.[21] Among colon cancer survivors, the O/E for subsequent primary colon cancer is 1.57 and for rectal cancer is 1.36 (Table 3). The O/E for all subsequent cancers is highest for colon cancer patients diagnosed with their initial cancer under age 40 (O/E = 2.77) and declines with age, with no overall increased risk among patients diagnosed at age 70 and older. Among patients diagnosed with colon cancer before age 40, the O/E is 12.46 for subsequent colon cancer, 12.24 for subsequent rectal cancer, 7.10 for cancer of the uterine corpus, 4.26 for ovarian cancer, and 3.17 for acute non-lymphocytic leukemia (Table 3).

Much of this increased risk for subsequent cancers among colorectal cancer patients diagnosed at an early age is related to two genetic susceptibility syndromes associated with early onset colon cancer mentioned previously: FAP and HNPCC, also known as Lynch syndrome. Both of these syndromes are inherited diseases in which carrier parents have a 50:50 chance of passing the mutation to each child.[22] FAP is due to an inherited defect that leads to the appearance of numerous (> 100) polyps throughout the large bowel, and usually becomes evident in the second decade of life. If untreated, patients typically develop colorectal cancer at a mean age of 39 years. FAP is responsible for < 1% of colon cancers. The risk of multiple

colon cancers is so high that the recommended treatment is removal of the entire colon at an early age in anyone identified with this syndrome. FAP is also associated with increased risk of cancer of the stomach, small intestine, thyroid, pancreas, and brain. HNPCC is characterized by early onset of predominantly right-sided colon cancer and the tendency to develop multiple cancers. Affected individuals generally develop only a few polyps, and these generally occur at a later age than in patients with FAP.[22] HNPCC families are defined by the occurrence of colorectal cancer in three relatives, one of whom is a first-degree relative of the other two, diagnosis of at least one of the colorectal cancers before age 50, involvement of at least two generations, and exclusion of FAP. HNPCC occurs as a result of mutations in genes that repair errors in DNA and is associated with approximately 3-6% of colorectal cancers in the US.[22] Affected individuals can now be identified using molecular approaches rather than relying exclusively on family history. HNPCC also predisposes to early-onset cancers of the small intestine, stomach, bile ducts, uterine corpus, ovary, renal pelvis, ureter, and brain.[21] Patients can be monitored with colonoscopy and do not require removal of the colon since the risk of colon cancer is less than in patients with FAP. Recommendations are available for identification, genetic screening and counseling, and colorectal cancer screening for individuals who may be at high risk of colorectal cancer because of recognized genetic syndromes, and for those whose family history indicates high risk without one of the identified factors.[23]

Risks of developing subsequent cancers among patients who have a history of rectal cancer are lower than those among patients with a history of colon cancer. Although rectal cancer survivors are not at increased risk of developing subsequent cancers of all types combined, they do have an elevated O/E for subsequent colon cancer (O/E=1.45), particularly if the first cancer is diagnosed at younger ages (Table 3).

In addition to the hereditary syndromes, survivors of colorectal cancer may be at increased risk of developing subsequent cancers because of common risk factors, including treatment with chemotherapy or radiation, diet, obesity, physical inactivity, and hormonal/reproductive factors. Since the overwhelming majority of subsequent cancers among colorectal cancer survivors occur in the colon and rectum, medical surveillance for these patients has the potential to detect recurrence and to detect new colorectal adenomas or cancers.[24] Colonoscopy is recommended one year after curative surgery for colon and rectal cancer; if that examination is normal, another colonoscopy is recommended at 3 years, and if that is normal, the next examination is at 5 years. In addition, since rectal cancer patients have a higher probability of local recurrence than colon cancer patients, surveillance sigmoidoscopy or endoscopic ultrasonography is recommended at 3- to 6-month intervals for the first 2 to 3 years after treatment.[24]

Tobacco-related cancer

Patients with primary cancers of sites related to tobacco use have an increased risk of developing subsequent cancers at tobacco-related sites. The SEER multiple primary study found that the O/Es for subsequent cancer among individuals with tobacco-related primary cancers are higher in women than in men (Table 4).[25, 26, 27] This difference is likely due to the fact that a much higher proportion of men than women in the general population are current or former smokers, and thus the rates of smoking-related cancers used to calculate the expected number of cancers are higher.[26] Among patients with primary lung cancer, subsequent lung cancers constitute almost a third of new primary cancers, with increases in risk being highest (greater than 3-fold) among patients surviving 5 or more years after initial diagnosis. Elevated O/Es among lung cancer survivors have also been observed for cancer of the oral cavity and pharynx, larynx, esophagus, bladder and renal pelvis, and ureter in men and women, and uterine cervix in women, as well as some other less common cancers. The risks of subsequent cancers of the lung and oral cavity are especially high among lung cancer survivors who continue to smoke cigarettes. Some data suggest that smoking cessation following lung cancer lowers the risk of new smoking-related cancers.[26]

Male survivors of laryngeal cancer have a relative risk of 1.62 for developing a subsequent cancer. The subsequent tumors associated with laryngeal cancer include lung, oral cavity and pharynx, and esophagus and likely result from joint exposure to tobacco and alcohol. The SEER study also found increased risk of subsequent cancers of adjacent sites among patients whose laryngeal cancer was treated with radiation.[26] Survivors of cancers of the oral cavity and pharynx have more than a 2-fold excess risk of developing a subsequent cancer, with especially high relative risks of subsequent cancers of the oral cavity and pharynx, esophagus, and larynx (Table 4). Tobacco and/or alcohol consumption probably account for much of the increased risk. Squamous cell carcinoma of the esophagus is strongly related to tobacco smoking and is also associated with alcohol abuse and low fruit and

Table 4. Observed-to-Expected Ratio for Developing Subsequent Tobacco-related Cancer after Selected Tobacco-related First Primary Cancers, SEER 1973-2005

Females

First primary cancer	Subsequent primary cancer: Lung	Oral cavity & pharynx	Larynx	Esophagus	Bladder	Kidney parenchyma	Renal pelvis & ureter	Uterine cervix	All subsequent cancers†
Lung & bronchus	3.81*	2.61*	5.03*	3.63*	1.92*	1.83*	1.71*	0.9	1.53*
Oral cavity & pharynx	4.59*	39.85*	12.88*	23.90*	1.32	1.02	0.88	1.47	2.47*
Larynx	7.01*	13.49*	7.22*	13.03*	1.64*	2.01*	1.16	1.56	2.38*
Esophagus‡	2.46*	28.74*	7.25*	5.50*	1.39	2.38	5.02	3.11	1.78*
Bladder	2.17*	1.00	2.04*	1.07	2.43*	1.64*	18.13*	0.75	1.31*
Kidney parenchyma§	1.17*	0.90	0.78	0.59	2.45*	5.50*	0.99	1.31	1.18
Renal pelvis & ureter	2.75*	1.73	3.33	1.10	47.90*	0.45	16.38*	0.36	2.96*
Uterine cervix	2.35*	1.76*	2.98*	1.66*	2.59*	1.11	3.01*	0.61*	1.25*

Males

First primary cancer	Subsequent primary cancer: Lung	Oral cavity & pharynx	Larynx	Esophagus	Bladder	Kidney parenchyma	Renal pelvis & ureter	All subsequent cancers†
Lung & bronchus	2.06*	2.26*	2.73*	2.29*	1.50*	1.58*	1.40*	1.32*
Oral cavity & pharynx	3.82*	18.31*	5.64*	12.50*	1.13	1.13	1.10	2.36*
Larynx	3.39*	5.27*	1.73*	3.63*	1.31*	1.27*	1.34	1.62*
Esophagus‡	2.05*	12.85*	4.41*	0.76	1.09	0.37	0.84	1.67*
Bladder	1.58*	0.92	1.31*	1.00	0.89*	1.44*	11.00*	1.20*
Kidney parenchyma§	0.97	0.69*	0.80	0.73	1.51*	3.98*	1.29	1.17*
Renal pelvis & ureter	1.85*	0.84	1.13	1.26	15.81*	1.05	18.37*	2.44*

Note: Excludes the first 2 months after initial cancer diagnosis. Site definitions are based on Appendix 2a and 2b from Curtis RE, Freeman DM, Ron E, et al., (eds.) *New malignancies among cancer survivors: SEER cancer registries, 1973-2000*. Bethesda, MD: National Cancer Institute, NIH Publ. No. 05-5302; 2006.

EAR = excess absoute risk per 10,000 person years at risk (PYAR); ANLL = acute non-lymphocytic leukemia.

* $p<0.05$

† All subsequent cancers excludes non-melanoma skin cancer.

‡ Squamous cell carcinoma of the esophagus.

§ Site definition includes age ≥ 20 years.

vegetable intake.[28] Patients with primary squamous cell carcinomas of the esophagus have a large excess risk for subsequent cancers of the oral cavity and pharynx, and of the larynx. Although HPV infection is the primary cause of cancer of the uterine cervix, increased risks of cervical cancer among smokers have been observed in many studies. HPV infection likely explains elevated risks of some anogenital cancers following oral and pharyngeal cancers and reciprocal excesses of oral cancer following cancers of the anus, cervix, vulva, and penis (data not shown).[25]

Patients with primary cancers of the bladder have a very high (>10-fold) excess risk of developing subsequent cancers of the renal pelvis and ureter with reciprocally elevated large excess risks of bladder cancer among patients with primary cancer of the renal pelvis and ureter (Table 4). Although transitional cell carcinomas of the bladder and

Table 5.Observed-to-Expected Ratio for Developing Subsequent Primary Cancer after Hodgkin and Non-Hodgkin Lymphoma by Age at Diagnosis of First Primary, SEER 1973-2005

Hodgkin lymphoma

Second primary site	Birth to 19 (N=3,026)	20 to 39 (N=10,272)	40-59 (N=4,365)	60 and older (N=3,352)	All ages (N=21,015)	Observed number	Expected number	EAR
Lung & bronchus	10.16*	5.07*	3.47*	1.78*	3.03*	365	120	11.34
Female breast	17.00*	2.99*	1.36*	1.04	2.50*	307	123	8.54
Non-Hodgkin lymphoma	7.49*	6.54*	6.83*	3.78*	5.86*	225	38	8.66
ANLL	31.86*	19.86*	18.16*	6.57*	15.24*	121	8	5.24
All subsequent cancers†	7.80*	2.87*	2.11*	1.28*	2.20*	2,013	917	50.85

Non-Hodgkin lymphoma

Second primary site	Birth to 19 (N=2,236)	20 to 39 (N=9,683)	40-59 (N=27,862)	60 and older (N=54,641)	All ages (N=94,422)	Observed number	Expected number	EAR
Lung & bronchus	–	2.37*	1.59*	1.18*	1.30*	1,449	1,115	6.52
Hodgkin lymphoma	4.13	5.65*	7.94*	3.85*	5.35*	99	18	1.57
ANLL	23.94*	12.13*	5.51*	2.38*	3.34*	212	63	2.90
Melanoma	2.08	1.61	1.42*	1.42*	1.44*	293	204	1.74
Kaposi sarcoma	–	15.31*	16.89*	2.34*	11.25*	119	11	2.12
All subsequent cancers†	4.55*	2.14*	1.34*	1.05*	1.16*	8,408	7,262	22.42

Note: Excludes the first 2 months after initial cancer diagnosis. Site definitions are based on Appendix 2a and 2b from Curtis RE, Freeman DM, Ron E, et al., (eds.) *New malignancies among cancer survivors: SEER cancer registries, 1973-2000*. Bethesda, MD: National Cancer Institute, NIH Publ. No. 05-5302; 2006.

EAR = excess absoute risk per 10,000 person years at risk (PYAR); ANLL = acute non-lymphocytic leukemia.

* $p<0.05$

† All subsequent cancers excludes non-melanoma skin cancer.

renal pelvis and ureter are known to be strongly related to tobacco smoking, a more modest (1.6 to 2.8-fold) excess risk is observed for subsequent lung cancers among survivors of cancers of the bladder and renal pelvis and ureter.

Primary prevention (tobacco avoidance) and tobacco cessation in smokers is the main strategy to reduce the burden of primary and secondary cancers related to tobacco. The high rates of subsequent primary cancers among patients who have been treated for head and neck and lung cancers led to attempts at chemoprevention. For example, several clinical trials have involved high doses of vitamin A in response to an earlier clinical trial that found that high doses of 13-cis-retinoic acid (vitamin A) were effective in reversing oral premalignant lesions (leukoplakia).[29] A subsequent phase II clinical trial in which patients were treated with 13-cis-retinoic acid, interferon alpha and alpha-tocopherol, and alpha had promising results but the phase III randomized trial was canceled because of persistent low recruitment.[30] An NCI trial of supplementation with high doses of vitamin A to prevent recurrence and second cancers among patients with early stage non-small cell lung cancer found no evidence of benefit in the population overall, but did find potential benefit for the subgroup of patients who were nonsmokers. Other chemopreventive agents have been tested with little or no evidence of benefit, but this remains an active area of research.[31]

Medical surveillance recommendations for lung cancer survivors focus on detection of recurrence and second primary lung cancers and include imaging studies (chest x-ray or CT) every 4-6 months in the first 2 years following diagnosis and then annually.[32] Surveillance for recurrence and subsequent primary tumors after primary tumors of the head and neck generally includes clinical examination, flexible fiberoptic nasopharyngeal endoscopy, and chest x-ray. [33]

Lymphomas

Lymphomas represent a family of tumors that arise from cells that are found in lymph nodes and other lymphoid tissues. There are many different forms of lymphoma that have different levels of aggressiveness and different treatments. Lymphomas are broadly classified as Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) based on the appearance of a specific cancer cell type called the Reed-Sternberg cell found in HL. Subsequent cancers among survivors of HL have been well-studied because of the high survival rate for the disease, the relatively young age at diagnosis, and the resultant long life expectancy. HL was also one of the earliest cancers for which effective treatments with radiotherapy and chemotherapy were developed. As a result, the 5-year relative survival rate increased from 74 % in 1975-1977 to 86% in 1996-2004. The SEER study found an O/E of 2.20 for all subsequent cancers among patients treated for HL (Table 5).[34] Survivors of HL had a substantially increased risk of lung cancer (O/E=3.03), which has been related in a dose-dependent fashion to both chemotherapy and radiation therapy. The risk of lung cancer was higher among HL survivors who smoked, compared to those who did not smoke. Substantially elevated relative and absolute risks were also observed among HL survivors for subsequent cancers of the female breast, non-Hodgkin lymphoma, and acute non-lymphocytic leukemia (Table 5). The risk of breast cancer among women treated with radiotherapy for HL increases with higher radiation doses to the breast, and occurs primarily among women treated for HL as young adults. Females ages 10 to 30 years who have been treated for HL with radiation therapy to the chest are included in high-risk groups for whom the American Cancer Society recommends MRI screening as an adjunct to mammography for breast cancer screening.[20] The increased risk of breast cancer among HL survivors treated with radiation therapy is moderated among women who also received alkylating agent chemotherapy, likely the result of treatment-related ovarian failure. The high O/E for acute non-lymphocytic leukemia (ANLL) (O/E=15.24) among HL survivors was first observed among patients treated in the 1970s and is thought to be related to the alkylating agent chemotherapy regimens used at the time.[34] An increased risk for NHL is also observed among HL survivors (Table 5); it is not known whether the increased risk is associated with therapy or other factors.[35]

NHL represents a broader range of diseases than HL. Risk factors and treatments for NHL can differ substantially, and the relative risk for subsequent cancers also depends on the specific type of NHL and the treatment used. As a group, survivors of NHL also have an increased O/E for developing subsequent cancers, but this risk is lower than for HL survivors (O/E=1.16). NHL survivors as a group also have increased risk for Kaposi sarcoma (O/E=11.25), HL (O/E=5.35), ANLL (O/E=3.34), melanoma (O/E=1.44), and cancer of the lung and bronchus (O/E=1.30). Some forms of NHL are increased in patients who are infected with HIV, and HIV also increases risk of Kaposi sarcoma.[34]

Melanoma

Ultraviolet radiation from the sun is associated with several types of skin cancer, including malignant melanoma. Although the incidence of basal and squamous cell skin cancer is not tracked by cancer registries in the US, many patients develop multiple skin cancers, commonly in sun-exposed areas. In the SEER study, the O/E for subsequent primary cancer among multiple melanoma survivors was 1.26, due primarily to excess risk of subsequent melanomas (O/E=8.63).[36] About 10% of patients who had a subsequent melanoma had 3 or more primary melanomas. In addition to ultraviolet radiation exposure, host susceptibility factors likely account for the increased risk of subsequent melanomas. The risk of multiple primary melanomas is greater among patients with a family history of melanoma or atypical moles. It is recommended that patients who have been treated for a malignant melanoma receive lifelong annual dermatologic follow-up and perform self-examinations. More intensive dermatologic surveillance may be recommended for patients who have had multiple melanomas, positive family history, or a history of atypical moles.[37]

Childhood cancer

Progress in treatment of childhood cancer has produced increasing numbers of childhood cancer survivors who are living into adulthood. Currently, more than 80% of children and adolescents with cancer survive 5 or more years after diagnosis. Unfortunately, the childhood cancer experience predisposes long-term survivors to a variety of long-term health problems, including increased risk of subsequent primary cancers.[38]

The SEER study found an O/E of 5.58 for subsequent cancer among childhood cancer survivors diagnosed at age 0 to 17 years (Table 6).[12] The highest O/Es were observed among patients initially diagnosed with Hodgkin lymphoma (O/E=9.21), primitive neuroectodermal tumors of the brain and central nervous system (O/E= 13.54),

Table 6. Observed-to-Expected Ratio for Subsequent Primary Cancer (All Sites Combined) Following Childhood Cancer (Aged 0-17 Years) by Type of First Cancer, SEER 1973-2005

First Primary Cancer	Male and female			Male			Female		
	Observed	O/E	EAR	Observed	O/E	EAR	Observed	O/E	EAR
All Cancers	**587**	**5.58***	**17**	**266**	**5.62***	**15**	**321**	**5.55***	**19**
Leukemia	84	4.64*	9	39	4.18*	8	45	5.12*	11
Acute lymphocytic	65	4.39*	9	32	4.09*	8	33	4.73*	10
Acute non-lymphocytic	10	5.34*	13	3	3.88	7	7	6.36*	17
Hodgkin lymphoma	149	9.21*	47	42	6.22*	24	107	11.36*	72
Non-Hodgkin lymphoma	25	5.49*	17	17	5.80*	17	8	4.92*	16
Brain & CNS	98	6.19*	17	60	7.65*	20	38	4.75*	14
Ependymoma	7	7.63*	18	6	12.69*	28	1	2.25	4
Astrocytoma	39	3.90*	10	25	5.12*	13	14	2.74*	7
PNET, brain & CNS	29	13.54*	34	17	15.09*	33	12	11.83*	34
Neuroblastoma	15	4.63*	8	6	3.64*	5	9	5.65*	10
Retinoblastoma	27	14.89*	28	15	17.16*	32	12	12.78*	24
Wilms tumor	21	5.20*	10	11	6.19*	11	10	4.42*	8
Bone & joints	44	7.16*	27	17	6.25*	20	27	7.89*	36
Osteosarcoma	23	6.30*	25	9	5.96*	19	14	6.54*	31
Ewing sarcoma	19	11.03*	39	8	9.62*	31	11	12.34*	49
Soft-tissue incl. heart	41	4.85*	15	17	4.23*	11	24	5.41*	20
Rhabdomyosarcoma	18	6.73*	18	9	5.97*	14	9	7.73*	23
Fibrosarcoma†	10	3.37*	11	2	1.6	2	8	4.65*	18
Other soft-tissue	13	4.70*	17	6	4.81*	15	7	4.62*	19
Germ-cell tumors	25	3.21*	10	14	4.16*	13	11	2.49*	8
Carcinomas/epithelial‡	41	2.64*	10	19	4.61*	18	22	1.93*	6
Other Codes§	20	5.52*	14	12	5.87*	14	8	5.06*	15

First primary cancer categorized using the International Classification of Childhood Cancer; O/E=observed to expected ratio; EAR= excess absoute risk per 10,000; CNS=central nervous system; PNET=primitive neuroectodermal tumor.

* p<0.05

† Also includes neurofibrosarcoma.

‡ Includes adrenocortical carcinoma, thyroid carcinoma, nasopharyngeal carcinoma, malignant melanoma, skin carcinoma other than melanoma, and other or unspecified carcinoma.

§ Includes Burkitt lymphoma, unspecified lymphoma, miscellaneous lymphoreticular cancers, other tumors of sympathetic nervous system, non-CNS PNET, renal carcinoma, hepatoblastoma, hepatic carcinoma, and other or unspecified cancers.

retinoblastoma (O/E=14.89), and Ewing sarcoma (O/E=11.03) (Table 6). Survivors of acute lymphocytic leukemia, the most common cancer in childhood, had a O/E of 4.39; most of this excess is due to subsequent cancers of the salivary glands, brain/central nervous system, bone, and thyroid gland. Cranial radiation given to prevent or treat CNS involvement may be associated with these excesses.[39] The most common types of second cancers occurring among childhood cancer survivors are cancers of the female breast, brain/central nervous system, bone, thyroid gland and soft tissue, as well as melanoma and acute non-lymphocytic leukemia (ANLL).[39] Secondary ANLL commonly develops in association with alkylating agent or topoisomerase II therapy; radiation exposure has also been linked to secondary leukemias, but risks are much lower. Radiation therapy contributes to excess risks for the solid tumors; data on the influence of chemotherapy as a contributor to subsequent solid tumors are more limited. Treatment for these tumors has been modified over the years to maximize efficacy and to minimize long-term risks, including secondary cancer. Secondary breast cancer is most strongly associated with radiation therapy to the chest for women treated between the ages of 10 and 30 years. Breast cancer incidence rates among women with such exposure starts to rise about 8 years after radiation treatment and continues to be elevated for more than 25 years. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography recommend annual MRI screening for women who received radiation therapy to the chest between the

ages of 10 and 30 years. For most women at high risk, the guidelines recommend screening with MRI and mammography beginning at age 30 and continuing for as long as the woman is in good health.[20]

Follow-up care for survivors of childhood cancers includes surveillance for recurrence of the original cancer or the development of a new cancer, assessing psychosocial needs, monitoring growth and maturation, counseling regarding preventive health, and testing for specific risk factors and late effects. The Children's Oncology (COG) group has published "Long Term Follow-up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers," which provides detailed information on late effects associated with childhood cancer and its treatment, identifies those at highest risk, and makes specific recommendations for periodic evaluations and health counseling. Since some late effects may not become apparent until adolescence or adulthood, models are available for coordinating care as the child transitions from active treatment and monitoring to longer-term follow-up, young adulthood, and adulthood. Some of the elements of survivorship plans developed in the context of childhood cancer may also be of value for adult patients.

Treatment Summaries and Survivorship Care Plans

It is important that patients diagnosed with cancer have information about their diagnosis, details of their treatment, and a recommended follow-up plan.[40] This plan should include information about recommended cancer screening, surveillance for recurrence, the schedule on which tests and examinations should be performed, information about possible late- and long-term effects of treatment and their symptoms, and possible signs of recurrence and second tumors. In addition to recommendations that are specific to their primary cancer, age at initial diagnosis, and potential risks related to treatment, it is important that cancer survivors follow the recommendations for cancer prevention and early detection in the general population, including tobacco avoidance or cessation, physical activity, nutrition and diet, healthy weight, and recommendations for cancer screening. [41]

American Cancer Society

Intramural Research

As noted previously, the number of people with a personal history of cancer living in the US has continued to rise, and is expected to double by the year 2030 to more than 20 million.[42] In response to the need to identify the quality-of-life concerns of this growing population, the American Cancer Society's intramural Behavioral Research Center designed and implemented a program of research known collectively as the Studies of Cancer Survivors (SCS).[43] The SCS are two large-scale, population-based, national studies of cancer survivors' quality of life: SCS-I and SCS-II. SCS-I enrolled more than 6,000 1-year survivors of 10 common cancers and is following this group for up to 10 years. In order to learn about the experience of longer-term survivors, SCS-II enrolled approximately 10,000 cancer survivors at either 3, 6, or 11 years following diagnosis. Because health behaviors impact the risk for subsequent cancers, one focus of research is lifestyle choices and behavior changes among survivors after their cancer diagnosis. One SCS-II study found that survivors demonstrated good compliance with the American Cancer Society recommendation to avoid tobacco products (82.6%–91.6%), but showed relatively poor compliance with the guidelines in the areas of physical activity (29.6%–47.3%) and consumption of fruits and vegetables (14.8%–19.1%).[44] Greater compliance with the recommendations was associated with a better quality of life among the survivors in this study. Future analyses planned for the SCS data include investigations of the prevalence, predictors, and impact of fear of cancer recurrence and patterns in the use of complementary and alternative medicine.

Extramural Research

The American Cancer Society's extramural grants program has supported research related to multiple primary cancers at various academic institutions across the country. Focus areas of recent research have included:

- The chemoprevention of secondary cancers in the head and neck
- Reducing the side effects of chemopreventive drugs, such as tamoxifen
- Expanding the knowledge about cancer susceptibility syndromes, such as Li-Fraumeni syndrome and familial adenomatous polyposis (FAP)
- Further understanding the excess cancer risk in childhood cancer survivors

Advocacy

The American Cancer Society Cancer Action Network℠ (ACS CAN), the nonprofit, nonpartisan advocacy affiliate of the American Cancer Society, supports evidence-based

policy and legislative solutions designed to eliminate cancer as a major health problem. ACS CAN has been an active participant in the development and dissemination of several Institute of Medicine reports that make policy and practice recommendations for addressing the barriers to survivorship care planning, coordination of care, and monitoring of late- and/or long-term post-treatment side effects in survivors. The health policy recommendations in these IOM reports form the backbone for federal bills ACS CAN supports through its advocacy work to promote prevention and care planning for patients as well as follow-up care for survivors. ACS CAN works to encourage elected officials and candidates to make cancer a top national priority. ACS CAN gives ordinary people extraordinary power to fight cancer with the training and tools they need to make their voices heard. For more information, visit acscan.org.

Programs

In order to better serve our constituents – particularly newly diagnosed patients and their caregivers, the American Cancer Society offers an integrated network of programs and services through the Cancer Resource Network. The network can provide constituents with information, day-to-day help, and emotional support they need to get well. These programs and services can be accessed through the Society's National Cancer Information Center, Division service centers, the cancer.org Web site, Patient Navigator Program and Cancer Resource Center sites, Employer Initiative, and by health care provider referrals. Using these services, constituents have access to not only the American Cancer Society's programs, but also other national, state, and local resources through the Society's Cancer Resource Connection, a repository of other organizations' programs and services.

The Society's Web site, cancer.org, offers information, online decision-making tools, and other resources to aid in patient care management, and also provides information on the prevention and early detection of cancer, as well as opportunities for community involvement. Staffed by volunteers and patient navigators (trained health professionals), Cancer Resource Centers are located in selected hospitals across the country. These services help the patient and caregiver navigate the various systems and overcome barriers to their care by improving access to information, services, programs, and referral to community resources.

The American Cancer Society's programs assist those touched by cancer – from newly diagnosed, in treatment, and through survivorship – with a wide array of offerings. The Hope Lodge® program can provide people who must travel to their treatment temporary lodging. The Society can also assist those trying to find a clinical trial, or access to health insurance specialists and legal guidance. Help is available with local transportation needs to treatment facilities through the Road to Recovery® program. For those individuals dealing with the physical impact of their treatment, products and services are available that improve appearance and self-esteem through the Look Good...Feel Better® and *"tlc"*™ programs. To assist in addressing the emotional support needs for breast cancer and prostate cancer patients and their family members, Reach to Recovery® and Man to Man® programs, along with the Cancer Survivors Network®, provide peer-to-peer support and education to improve the quality of life in group, individual, face-to-face, phone, or online settings.

Data Sources

The observed-to-expected ratio (O/E) and estimated absolute risk (EAR) are calculated using a cohort study approach in which individuals with a specific first cancer are followed over time to examine the risk of developing a subsequent primary cancer. Person-years-at-risk (PYAR) of developing a subsequent cancer are counted from the date two months after the diagnosis of the first cancer (to exclude multiple primaries diagnosed at the same time) until the date of last known vital status or death, and allocated by age, sex, race, and calendar year. The number of expected cancers is calculated for each PYAR stratum using cancer incidence rates from the referent (SEER) population, and then summed over all strata. The O/E is calculated by dividing the observed number of cancers by the expected number; statistical significance and confidence intervals are calculated using standard methods.[45] The O/E is used to identify increased or decreased risks of developing another cancer. The EAR is obtained by subtracting the expected number of cancer cases from the observed number of cancer cases, dividing by the PYAR, and multiplying by 10,000 to yield the number of excess cancers per 10,000 PYAR. The EAR is a useful measure of the impact of the subsequent cancer in a population of cancer patients. Statistical methods have also been developed to estimate the total number of cancer survivors in the US by primary site and the number who have been diagnosed with more than one cancer.[46]

Certain methodological limitations should be considered when interpreting data on multiple primaries from population-based registries and other population groups. Cancer patients are often under closer medical surveillance than the general population, which could lead to earlier detection of asymptomatic cancers that would not have been clinically evident for several years, or possibly not detected during the patient's lifetime. Apparent reduced risk of subsequent cancers may occur when surgery removes one or more organs from risk (such as removal of the uterus and ovaries for gynecologic cancer) or when multiple primary tumors of the same organ are considered single primaries (such as multiple cancers in the prostate and urinary bladder). Another limitation of studies in geographically defined areas, such as the SEER registries, is that subsequent cancers are not recorded for patients who migrate from their original geographic areas. This leads to under-ascertainment of cancer cases and conservative (negatively biased) estimates of cancer risk, which may be stronger for younger patients and those from more mobile populations.[47]

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