Chapter 1
Introduction

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Survival from cancer has improved dramatically as a result of recent advances in the treatment of cancer and its detection at an early stage. In the U.S., 5-year relative survival rates for all cancers combined increased steadily, from 50% in 1975-1979 to 66% in 1996-2002 among adults, and from 61% to 79% among children (Ries et al, 2006). Moreover, 10-year survival rates are approaching 59% in adults and 75% in children. As of January 1, 2003, about 10.5 million people in the U.S. were living with cancer (Ries et al, 2006). For some, the improvements in survival have come at a cost, however, in the form of long-term physical and psychosocial consequences of the disease and its treatment. A fuller understanding of these late effects has been achieved by an expanded research and policy agenda in cancer survivorship in the U.S. (Aziz and Rowland, 2003; Hewitt et al, 2003, 2005; CDC and LAF, 2004; NCI, 2004). Among the major medical concerns for cancer survivors is the risk of developing new primary cancers. It has been estimated that among those cancer survivors alive as of January 1, 2002, at least 750,000 (nearly 8%) had more than one form of cancer diagnosed between 1975 and 2001 (Mariotto, 2006). As a result, there is a growing need for a national system of population-based statistics to monitor the risk of developing new malignancies among long-term survivors of cancer.

Twenty years have passed since the publication of the National Cancer Institute (NCI) monograph titled *Multiple Primary Cancers in Connecticut and Denmark,* a comprehensive survey of two populations with long-standing cancer registries (Boice et al, 1985). This study was useful in characterizing the site-specific risks of second cancers and suggesting clues to underlying causal factors shared by constellations of multiple cancers and to the carcinogenic potential of treatment modalities. The current monograph builds and expands on that earlier work by reporting on more contemporary patterns of multiple cancers across the U.S. population and suggesting explanations based on our current understanding of cancer causation through epidemiologic research. Herein we report on the risk of new malignancies that have arisen among cancer survivors for the 27-year period 1973 to 2000, utilizing data from NCI's Surveillance, Epidemiology and End Results (SEER) Program (NCI, 2006).

Abbreviations: O=observed number of subsequent (2nd, 3rd, etc.) primary cancers; O/E=ratio of observed to expected cancers; CI=confidence interval; PYR=person-years at risk; EAR=excess absolute risk (excess cancers per 10,000 person-years, calculated as [(O-E)/PYR]×10,000).

The SEER Program represents a unique population-based resource for evaluating the risk of subsequent cancers due to its large size, long follow-up of cancer survivors, and largely representative sample covering more than 10% of the U.S. population. With chapters organized according to the initial site of cancer, this monograph reports on the risks of subsequent malignancies for more than 50 adult and 18 childhood tumors, including new data on some uncommon sites and individual histologic types. The risks of subsequent cancers are systematically examined by gender, age at diagnosis of the initial cancer, and time since diagnosis, as well as the initial treatment and histologic type of certain cancers. Whenever relevant, the differences in subsequent cancer risk are noted by racial group (black and white); a subsequent publication will examine the racial and ethnic patterns in more detail. This monograph is intended primarily to provide new incidence data, rather than a comprehensive review of the literature on multiple primary cancers (Neugut et al, 1999; van Leeuwen and Travis, 2005; Schottenfeld and Beebe-Dimmer, 2006). However, in each chapter, the patterns of multiple cancers observed are compared with findings from other studies and discussed in terms of potential risk factors and mechanisms. In addition, efforts are made to cite previous analyses of second cancers that utilized SEER data for specific tumors covered in this monograph.

Overall Risks of Subsequent Cancers

Based on the 9 original cancer registries, the SEER Program provided data on more than 2 million cancer patients who survived at least 2 months (including nearly 390,000 patients surviving at least 10 years and 76,000 patients surviving 20 or more years), yielding close to 11 million person-years at risk over the follow-up period from 1973 to 2000. Overall, we found that cancer survivors had a 14% higher risk of developing a new malignancy than would have been expected in the general SEER population (O/E=1.14, 95% CI=1.14-1.15) (Table 1.A). A total of 185,407 new primary cancers were observed compared with 162,602 expected. (The risk of subsequent prostate cancers diagnosed following an initial prostate cancer was excluded from the analysis, since typically these second tumors are not reportable to SEER.) The

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Table 1.A: Risk of subsequent primary cancer after any initial cancer, by age at initial diagnosis, SEER 1973-2000.

Age at initial diagnosis	Total			Males			Females		
	O	O/E	EAR	O	O/E	EAR	O	O/E	EAR
All ages	**185,407**	**1.14***	**21**	**100,428**	**1.11***	**22**	**84,979**	**1.17***	**21**
00–17	351	6.13*	15	176	6.44*	15	175	5.84*	15
18–29	1,401	2.92*	22	562	3.39*	22	839	2.67*	23
30–39	4,909	2.37*	39	1,530	2.88*	40	3,379	2.20*	38
40–49	13,537	1.61*	39	4,466	1.83*	52	9,071	1.52*	34
50–59	34,159	1.27*	32	15,957	1.33*	46	18,202	1.21*	24
60–69	62,286	1.13*	23	35,986	1.11*	25	26,300	1.14*	22
70–79	52,321	1.02*	4	32,419	1.00	0	19,902	1.05*	9
80–115	16,443	0.92*	-19	9,332	0.92*	-26	7,111	0.93*	-14

Notes: All first primary cancers, except for non-melanoma skin, are included in the analysis. Subsequent cancers include 2nd, 3rd, and later primaries and encompass all cancer sites, except for non-melanoma skin and subsequent prostate cancers following first primary prostate cancer. Due to their large impact on subsequent cancer risks for males, O, O/E, and EAR were adjusted by excluding observed and expected numbers of subsequent prostate cancers following an initial prostate cancer (O=44, E=15,185). The population at risk includes 2,036,597 patients who survived 2 or more months after initial diagnosis during 1973 to 2000 (1,038,089 males and 998,508 females, 9 SEER registries). Numbers of patients surviving at least 5, 10, and 20 years were 789,221, 387,436, and 75,859 patients, respectively. The age distribution at initial diagnosis was 3.4%, 14.2%, 44.2%, 25.6%, and 12.6% for age groups <30, 30-49, 50-69, 70-79, and ≥80 years, respectively. The average age at initial cancer diagnosis was 64.6 years for men and 62.5 years for women.

Abbreviations: O=observed number of subsequent (2nd, 3rd, etc.) primary cancers; E=expected numbers of subsequent cancers; O/E=ratio of observed to expected cancers; PYR=person-years at risk; EAR=excess absolute risk (excess cancers per 10,000 person-years, calculated as [(O-E)/PYR]×10,000).

*P <0.05.

estimate of the excess absolute risk (EAR) among all patients combined was 21 excess subsequent cancer cases per 10,000 person-years. A very large proportion (93%) of the patients with multiple cancers had microscopic confirmation of each malignancy (first, second, and subsequent cancers), reflecting the high reliability of the SEER database and the low likelihood that metastatic spread from the original malignancy would be reported as a new primary cancer.

For most cancer sites, we examined the subsequent cancer risk according to age at diagnosis. As shown in Table 1.A, striking differences were observed by age, with relative risks surpassing 6-fold for survivors of childhood cancer (O/E=6.13). This finding is consistent with previous studies of childhood tumors, which have implicated initial therapy and genetic susceptibility as major risk factors for new cancers (Neglia et al, 2001; Bhatia, 2005). An age effect was further illustrated by the 2- to 3-fold increased risks for patients diagnosed as young adults (ages 18-39 years), and by the 1.2- to 1.6-fold elevated risks for those ages 40-59 years. In contrast, the observed number of new malignancies was lower than expected for survivors whose first cancer occurred at older ages (ages ≥80 years, O/E=0.92), which may be due to underreporting of second cancers among elderly patients related to competing risks from comorbid conditions and shortened life expectancies. In the combined analysis of all initial cancer sites, we found that the greatest burden of new malignancies was experienced by cancer patients initially diagnosed at ages 30 to 59 years, with EARs ranging from 32 to 39 per 10,000 person-years.

Overall, females had a slightly higher relative risk than males for all subsequent cancers combined (O/E=1.17 for females, versus 1.11 for males) (Table 1.A). However, the risk for males consistently exceeded that for females among patients whose initial cancer occurred before age 60 years. Similar patterns by age and sex were seen in analyses that excluded gender-specific initial cancers (cancers of the breast and genital tract), with the overall relative risk of developing a new malignancy being nearly equivalent among females (O/E=1.25) and males (O/E=1.22). For all ages combined, blacks had much higher risks of developing a new malignancy when compared with whites (blacks: O/E=1.31, EAR=46; whites: O/E=1.13, EAR=20). The racial differences in risk persisted among women and men in practically all age groups, indicating the need for further analyses that take into account racial differences in stage of disease, initial treatment, and other potential confounders.

In analyses by time after initial diagnosis and calendar year, we found that risks of new cancers were highest in the first 5 years after diagnosis and tended to decline somewhat among long-term survivors (Table 1.B). Heightened medical surveillance during the early follow-up period may partly explain the early excess, while lower risks in later follow-up intervals may be influenced by underascertainment of second malignancies for cancer survivors who migrate out of SEER geographic areas, and possibly by changes in behavioral patterns. In the most recent calendar year period (initial cancers diagnosed from 1995 to 2000), there was evidence of a higher rate of new malignancies compared with earlier periods with equivalent follow-up intervals, although longer surveillance will be needed to confirm this pattern.

In each chapter of this monograph, we estimated the percentage of patients diagnosed with a first primary cancer who developed a second cancer over time. For all cancers combined, nearly 14% of SEER patients developed a second cancer by 25 years of follow-up (cumula-

Table 1.B: Risk of subsequent primary cancer after any initial cancer, by calendar year at initial diagnosis and time since initial diagnosis, SEER 1973-2000.

	Years after first primary cancer diagnosis													
	<1 year		1-4 years		5-9 years		10-14 years		15-19 years		≥20 years		Total	
Calendar year of diagnosis	O	O/E	O	O/E	O	O/E	O	O/E	O	O/E	O	O/E	O	O/E
Relative risks (O/E ratios)														
1973–79	3,701	1.17*	12,375	1.18*	11,258	1.13*	8,861	1.08*	6,846	1.05*	4,355	1.05*	47,396	1.12*
1980–84	3,566	1.16*	12,086	1.17*	11,035	1.13*	8,429	1.14*	4,109	1.11*	87	1.03	39,312	1.14*
1985–89	4,493	1.16*	15,732	1.15*	14,208	1.13*	7,071	1.12*	167	1.21*	—	—	41,671	1.14*
1990–94	5,744	1.18*	19,320	1.13*	12,493	1.13*	295	1.24*	—	—	—	—	37,852	1.14*
1995–2000	6,512	1.28*	12,208	1.17*	456	1.29*	—	—	—	—	—	—	19,176	1.21*
Absolute excess risks (EARs)														
	O	EAR	O	EAR	O	EAR	O	EAR	O	EAR	O	EAR	O	EAR
1973–79	3,701	21	12,375	23	11,258	18	8,861	13	6,846	8	4,355	9	47,396	17
1980–84	3,566	22	12,086	24	11,035	20	8,429	23	4,109	19	87	6	39,312	22
1985–89	4,493	23	15,732	23	14,208	20	7,071	20	167	37	—	—	41,671	22
1990–94	5,744	28	19,320	20	12,493	21	295	42	—	—	—	—	37,852	21
1995–2000	6,512	40	12,208	25	456	45	—	—	—	—	—	—	19,176	30

Notes: All first primary cancers, except for non-melanoma skin, are included in the analysis. Subsequent cancers include 2nd, 3rd, and later primaries and encompass all cancer sites, except for non-melanoma skin and subsequent prostate cancers following first primary prostate cancer. O, O/E, and EAR were adjusted by excluding observed and expected numbers of subsequent prostate cancers following an initial prostate cancer (O=44, E=15,185). The population at risk includes 2,036,597 patients who survived 2 or more months after initial diagnosis during 1973 to 2000, 9 SEER registries.

Abbreviations: O=observed number of subsequent (2nd, 3rd, etc.) primary cancers; E=expected numbers of subsequent cancers; O/E=ratio of observed to expected cancers; PYR=person-years at risk; EAR=excess absolute risk (excess cancers per 10,000 person-years, calculated as [(O-E)/PYR]×10,000).

*P <0.05.

tive incidence of 5.0%, 8.4%, 10.8%, and 13.7% at 5, 10, 15, and 25 years, respectively). The cumulative incidence also varied markedly by age at initial cancer diagnosis, with the overall frequency of second cancers being highest among those diagnosed between 50 and 69 years of age (16.4% at 25 years of follow-up). Children (ages <18 years) experienced a 3.5% cumulative incidence of second cancer at 25 years, but further increases are expected as the young survivors (maximum age <45 years at the end of current follow-up) enter the period of rising cancer incidence.

Patterns of Multiple Primary Cancers

Although a sizable fraction of multiple cancers in the SEER database represented multicentric or multifocal tumors arising in the same site or organ system, most of the tumor constellations affected diverse organ sites. Whenever an excess risk of subsequent cancer was observed, a search was made for a reciprocal association that might suggest the presence of an underlying risk factor predisposing to multiple cancers. Of course, follow-up would be insufficient to detect risks among patients initially diagnosed with cancers that are often rapidly fatal (e.g., pancreas, liver).

Multicentric Tumors Versus Multiple Tumors of Diverse Sites—New malignancies that occurred in the same site or organ as the first primary cancer accounted for 13.2% of the 185,407 subsequent cancers occurring among patients in SEER surviving 2 months or more, with new tumors in the female breast (O=13,428; 7.2%), colon (O=3,630; 2.0%), lung (O=3,346; 1.8%), as well as melanoma of the skin (O=1,579; 0.9%) making up the large majority of the cases. While multicentric tumors are likely to reflect shared exposures and/or genetic predisposition, it is possible that heightened medical surveillance and mistaken diagnoses of cancer recurrence may play a role in some cases. An additional 3.8% of new malignancies originated in neighboring tissues or organs, at least partly from a "field cancerization" process whereby carcinogenic exposures and susceptibility states contribute to multicentric tumors that occur, for example, along the upper aerodigestive tract, the colon and rectum, and the lower urinary tract. Recent molecular studies of head and neck tumors and urinary tract cancers have indicated that multicentric involvement may actually result from the spread and implantation of a single clone of mutated cells (Tabor et al, 2002; Habuchi, 2005).

However, the majority of multiple primary cancers reported in the SEER database (more than 80%) arose in separate or independent organ systems. While a certain fraction of the subsequent tumors would be expected to develop at the same rate as in the general population, the patterns of excess risk that emerged are sufficiently distinctive to suggest risk factors that may be shared by the primary and subsequent tumors, or an effect of cancer therapies that are potentially carcinogenic. In interpreting the findings, however, one must consider the potential biases that may be introduced by diagnostic and reporting inaccuracies and other methodologic limitations of second cancer studies that are discussed in the next chapter.

Table 1.C: Risk of subsequent primary cancers following first primary cancers that are strongly related to tobacco and/or alcohol exposure (oral cavity and pharynx, esophagus, larynx, lung, and bronchus), by sex, SEER 1973-2000.

Subsequent primary cancer	Total			Males			Females		
	O	O/E	EAR	O	O/E	EAR	O	O/E	EAR
All subsequent cancers	24,688	1.64*	114	17,491	1.58*	120	7,197	1.82*	105
Oral/pharynx, esophagus, larynx, and lung/bronchus	11,593	3.62*	99	8,184	3.20*	105	3,409	5.33*	90
Oral/pharynx	2,510	9.04*	26	1,742	7.78*	28	768	14.29*	23
Larynx, lung/bronchus	8,084	2.95*	63	5,704	2.62*	66	2,380	4.26*	59
Esophagus	999	5.49*	10	738	4.74*	11	261	9.94*	8
Bladder, renal pelvis, ureter, and kidney parenchyma	1,772	1.44*	6	1,449	1.39*	8	323	1.71*	4
Bladder, renal pelvis, ureter	1,325	1.42*	5	1,116	1.38*	6	209	1.68*	3
Kidney parenchyma	447	1.48*	2	333	1.40*	2	114	1.78*	2
Pancreas	531	1.36*	2	346	1.28*	1	185	1.55*	2
Cervix uteri	60	1.16	<1	—	—	—	60	1.16	<1
Stomach	474	1.39*	2	395	1.44*	2	79	1.17	<1
All other cancers	10,258	1.05*	5	7,117	1.03*	4	3,141	1.08*	8

Notes: The population at risk includes 336,929 patients who survived 2 or more months after an initial diagnosis of cancer of the oral cavity/pharynx, esophagus, larynx, or lung/bronchus during 1973 to 2000 (221,000 males and 115,929 females, 9 SEER registries). Cancers of the oral cavity/pharynx are defined to include cancers of the tongue, tonsil, mouth/floor of mouth, oropharynx, and hypopharynx. All subsequent cancers include 2nd, 3rd, and later primaries and encompass all cancer sites, except for non-melanoma skin.

Abbreviations: O=observed number of subsequent (2nd, 3rd, etc.) primary cancers; E=expected numbers of subsequent cancers; O/E=ratio of observed to expected cancers; PYR=person-years at risk; EAR=excess absolute risk (excess cancers per 10,000 person-years, calculated as [(O-E)/PYR]×10,000).

*P <0.05.

Tobacco and Alcohol—Tobacco smoking and alcohol intake are major causes of cancer in the general population and also appear to account for a sizable proportion of the new malignancies among cancer survivors (Vineis et al, 2004; Boffetta et al, 2006). More than 11,000 of the 25,000 subsequent cancers observed following initial cancers that are typically related to tobacco and/or alcohol (e.g., oral cavity/pharynx, esophagus, larynx, and lung) occurred at a variety of sites also related to these exposures (Table 1.C). In terms of absolute excess risk, tobacco/alcohol-related cancer sites accounted for about 10,000 excess subsequent cancers or more than 35% of the total excess subsequent cancers occurring in this survey (initial cancer sites with O/E>1.0). The rate of excess cancers (EAR) was estimated at 114 cases per 10,000 person-years. More detailed data provided in this monograph suggest a differential effect of tobacco or alcohol when the initial cancers are analyzed by histologic type (e.g., squamous cell carcinoma versus adenocarcinoma of the esophagus), by cancer subsite (e.g., renal pelvis versus renal parenchyma), or by earlier age at initial diagnosis (e.g., ages <70 versus ≥70 years). The impact of tobacco and alcohol on the risk of second cancers is also evident in the risk reductions that have been reported with cessation of exposures after the initial cancer diagnosis (Do et al, 2004).

Nutrition and Hormones—Although we could not directly measure the impact of diet, obesity, physical inactivity, reproductive, and other lifestyle risk factors on the incidence of subsequent tumors in our survey, it seems likely that these factors contributed to the excess risk of new malignancies we and others have observed among patients with cancers of the female breast, reproductive organs, and the upper and lower digestive tract (Henderson and Feigelson, 2000; Calle et al, 2003; Key et al, 2004, Pike et al, 2004; Samanic et al, 2006). For example, along with tobacco and alcohol, low consumption of fruits and vegetables may have influenced the risk of multicentric tumors along the upper aerodigestive tract, while caloric excess, obesity, physical inactivity, and reproductive factors probably contributed to the constellation of hormone-dependent tumors (breast, uterine corpus, ovary, and prostate), as well as cancers of the large bowel.

Infections and Immunosuppression—There is growing awareness that certain infectious agents (e.g., human papillomavirus [HPV], human immunodeficiency virus, human herpesvirus 8, Epstein-Barr virus, hepatitis B and C, Helicobacter pylori) as well as altered immune regulation and inflammation may have contributed to certain combinations of tumors (Hisada and Rabkin, 2005; Morgan et al, 2006). For example, cancers of the cervix and anogenital tract were likely to occur together as a result of HPV infections and underlying immunologic defects. The combination of anal tumors and tonsillar cancers also appeared to reflect HPV infections. With lymphoproliferative tumors such as chronic lymphocytic leukemia, the accompanying immune dysfunction probably contributed to the excess risks of certain cancers, such as cutaneous melanoma, as reported also in immunosuppressed transplant recipients.

Genetic Predisposition—Because heritable cancers tend to present earlier in life than sporadic tumors, the detailed analyses of risk by age at diagnosis, along with the find-

ing of reciprocal associations, may point to underlying genetic susceptibility (Garber and Offit, 2005). In particular, some constellations of tumors found in our study appeared to be manifestations of a familial cancer syndrome. Following early-onset colon cancer, the excess risks of cancers of the uterine corpus, ovary, bile ducts, small intestine, and renal pelvis resemble features of hereditary nonpolyposis colon cancer (Lynch syndrome), due to inherited mismatch repair genes (Umar et al, 2004). Among younger women with breast cancer, the remarkably high risks of contralateral breast and ovarian cancer are consistent with heritable syndromes associated with germline mutations of BRCA1/2 (Thompson and Easton, 2004). In addition, the association of breast cancer, sarcomas, and certain other cancers in children and young adults may reflect the occurrence of Li-Fraumeni syndrome, related mainly to germline mutations of p53 (Hisada et al, 1998). In clarifying the role of genetic susceptibility in multiple primary cancers, special insights have come from population-based family surveys of cancer carried out in Utah (Goldgar et al, 1994) and Sweden (Hemminki and Boffetta, 2004).

Treatment Effects—The overall data from the monograph suggested that cancer therapy among older adults was not associated with a substantial increase in subsequent cancer risk. In contrast, children and young adults seemed to be especially prone to the carcinogenic effects of intensive radio-chemotherapy regimens (Bhatia, 2005; van Leeuwen and Travis, 2005). Children who survived 5 or more years after initial radiotherapy had the greatest risks of solid tumors, in keeping with the long latency typically seen for radiogenic solid cancers. In young adults, radiation contributed to the heightened risk for solid tumors arising in the fields of intense radiation exposure. Especially pronounced were the elevated risks of breast, lung, and other cancers among patients given radiotherapy for Hodgkin lymphoma. Although radiogenic cancers were not common following most adult-onset malignancies, excess risks were seen for cancers of the lung and esophagus, as well as sarcomas, following initial radiotherapy for breast cancer, while elevated risks were noted for acute leukemia after pelvic irradiation for cancers of the cervix and uterine corpus. Although the effects of chemotherapy and hormonal therapy were not directly assessed in our survey, markedly elevated risks of acute leukemia were observed following several cancers that have been generally treated with agents that are potentially leukemogenic. Among breast cancer patients, hormonal therapy (primarily tamoxifen) appeared to increase the incidence of cancer of the uterine corpus while decreasing the risk of contralateral breast cancer.

Future Directions

The results from the SEER Program and other surveys reported in the literature show clearly that the burden of second cancer occurrence is not borne equally among all cancer survivors. Instead, there are specific constellations of multiple tumors, so that it is possible to tailor strategies for primary and secondary prevention, including long-term medical surveillance aimed at the early diagnosis and treatment of subsequent tumors. The lowering of second cancer risk reported among survivors who changed their high-risk behaviors, most notably by cessation of smoking and alcohol drinking, indicates the need for behavioral research and educational programs to reinforce the importance of lifestyle changes that curtail exposure to cancer risk factors (Bellizzi et al, 2005; Pinto and Trunzo, 2005). While further work is needed to identify the causal factors underpinning some combinations of multiple cancers (e.g., thyroid and renal cancers), it seems reasonable that dietary and physical activity programs aimed at reducing excess body weight should also help lower not only the risk of a first primary cancer, but also the risk of subsequent cancers, along with increasing fruit and vegetable intake, reducing exposures to carcinogens in the workplace and environment, and limiting exposure to ultraviolet light and ionizing radiation whenever possible.

In addition to identifying the role of shared risk factors, studies of multiple primary cancers have been invaluable in detecting the late effects of cancer therapy, including leukemia and solid tumors, so that risk-benefit calculations can be made and appropriate patient groups identified for preventive interventions, including screening for new malignancies and chemopreventive strategies (van Leeuwen and Travis, 2005). The emergence of solid tumors as a late consequence of certain cancer therapies indicates the importance of long-term surveillance for subsequent cancers in SEER and other cancer registries, followed by case-control studies of tumors that occur excessively. Special emphasis should be placed on long-term follow-up of patients enrolled in clinical trials so that precise treatment details are available to monitor the potential adverse effects of specific therapies, which can then be weighed against their benefits. The results should inform clinical decision-making and the search for improved treatments that result in better survival rates as well as fewer late effects.

Several of the multiple cancer patterns presented in this monograph appear to reflect the activity of high-penetrant gene mutations that also underlie hereditary cancer syndromes (Garber and Offit, 2005). The challenge now is to identify the more common low-penetrant gene polymorphisms involved in modifying the carcinogenic risks of lifestyle and other environmental exposures, including the risks of radiation- and chemotherapy-related cancers. The recent report of an NCI workshop on cancer survivorship outlined the clinical, epidemiologic, molecular, and interdisciplinary research strategies that will enable a more complete understanding of the role of genetic predisposition in new malignancies among cancer survivors (Travis et al, 2006). Because recent advances in genomic and molecular sciences can now be incorporated into epidemiologic research, it should be possible to

illuminate the mechanisms of susceptibility to multiple cancers and provide insights into the long-term medical care and preventive interventions that will benefit the growing population of cancer survivors.

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