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Multiple Primary Cancers in Connecticut, 1935-82

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Recently, the National Cancer Institute published a comprehensive monograph on multiple primary cancers in Connecticut and Denmark [1]. This paper summarizes some of the observations made on the Connecticut population. Data compiled by the Connecticut Tumor Registry have extended our knowledge about the patterns of multiple primary cancers, especially among long-term survivors of cancer and among patients with relatively rare tumors about which little information currently exists. When compared with the general Connecticut population, cancer patients had a 31 percent (RR = 1.31) increased risk of developing a second cancer and a 23 percent (RR = 1.23) elevated risk of second cancer at a different site from the first. Common environmental exposures seemed responsible for the excess occurrence of many second cancers, particularly those related to cigarette smoking, alcohol consumption, or both. For example, persons with epithelial cancers of the lung, larynx, esophagus, buccal cavity, and pharynx were particularly prone to develop new cancers in the same or contiguous tissue throughout their lifetimes. Cancers of the colon, uterine corpus, breast, and ovary frequently occurred together, suggesting underlying hormonal or dietary influences. Only patients with prostate cancer were at significantly low risk for second cancer development; this might be an artifact of case finding, since advanced age at initial diagnosis was generally associated with an underascertainment of second cancers. Radiotherapy may have caused rectal and other cancer among patients with cancers of the female genital tract, and leukemia among patients with uterine corpus cancer. Chemotherapy with alkylating agents probably contributed to the excess of acute non-lymphocytic leukemia following multiple myeloma or cancers of the breast and ovary. Genetic susceptibility seemed to explain some tumor complexes, such as the multiple occurrences of cutaneous melanoma and the excess of bone cancer following retinoblastoma. Research into multiple cancer syndromes should enhance our understanding of carcinogenic factors and mechanisms and the development of strategies for cancer prevention and control.

INTRODUCTION

A comprehensive monograph on the risk of developing multiple primary cancers has recently been prepared by the National Cancer Institute in conjunction with the Connecticut Tumor Registry and the Danish Cancer Registry [1]. The reader interested in more details on the historical review, subjects and methods, results, and discussion is referred to this volume. Our paper attempts to provide an overview of the major findings with emphasis on results of interest to the Connecticut community. This monograph is the source of material for the sections following.

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SUMMARY OF MONOGRAPH FINDINGS

All First Cancers Combined

Data from 253,536 Connecticut patients diagnosed with an invasive cancer during 1935 to 1982 who survived at least two months without developing a simultaneous primary were combined so that their collective risk of second primary cancer over time could be examined [2]. More than 1,100,000 person-years of follow-up were accumulated for an average of 4.5 years per person. Both the first and second cancers were microscopically confirmed 88 percent of the time. A new primary neoplasm developed in 16,727 (6.6 percent) patients, whereas 12,797 second cancers were expected on the basis of rates from the general Connecticut population. Thus, patients with one cancer had 1.31 times the risk [95 percent confidence interval (CI) = 1.29–1.33] of developing a new independent primary compared with Connecticut residents without cancer. This relative risk (RR) is remarkably similar to the 1.29 risk estimate reported from Schoenberg's earlier Connecticut study (1935–1964), although almost twenty additional years of cancer diagnoses and follow-up were added to the Connecticut data base [3]. The risk of developing a second cancer was 14.7 per 1,000 persons per year, and the excess risk, i.e., after removing the expected incidence based on population rates, was 3.5 per 1,000 persons per year.

Connecticut residents with cancer remained at increased risk for a new malignant neoplasm throughout their lifetimes. Moreover, the risk increased from 1.29 during their first twenty years of follow-up to 1.49 for the 12,515 individuals surviving more than twenty years. Thirty-year survivors (2,218 patients, mostly female) continued to develop new second cancers at a high rate (RR = 1.45). Overall, 3,930 excess cancers developed over what would normally be expected in this population; 1,242 excess cancers (4.6 per 1,000 per year) developed after ten or more years of follow-up.

Females were more likely than males to develop a second cancer: RR = 1.42 versus 1.19 (Fig. 1). However, this difference was only apparent in the first twenty years of survival. Second cancers of the breast and gynecologic organs were responsible for a

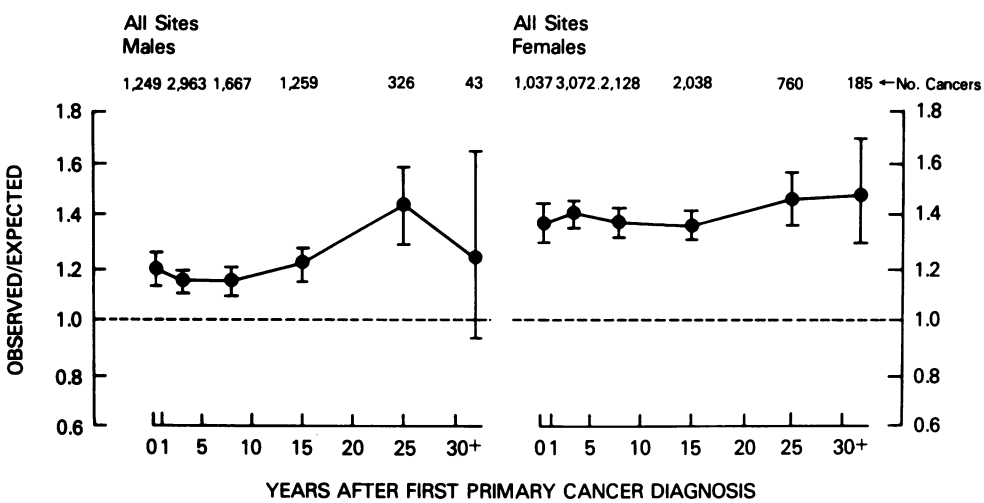

FIG. 1. Observed/expected ratios for all second cancers by time since diagnosis of any initial primary cancer and by sex. 95 percent confidence intervals are presented.

TABLE 1
Etiologic Factors Involved in Multiple Primary Cancers*

Etiologic factors	Associated cancer sites
Environmental, endocrine, or genetic risk factors	
Tobacco or alcohol consumption, or both	Cancers of the respiratory and upper digestive tracts
Endocrine or dietary factors, or both	Multicentric cancers of the colon; bilateral breast cancer; and clusters of cancers of the breast, uterine corpus, ovary, and colon
Genetic predisposition	Retinoblastoma and osteosarcoma, among others
Treatment effects	
Radiation	Cancer of the rectum following cervical cancer, among others
Chemotherapy	ANLL following Hodgkin's disease, NHL, multiple myeloma, and cancers of the ovary, breast, gastrointestinal tract, and lung, and childhood cancers
Hormones	Cancer of uterine corpus following breast cancer
Immunologic defects	Melanoma following chronic lymphocytic leukemia, among others

*Slightly modified from text–Table 1 [4]

large part of the sex differential in risk. Other sites for which the RR of second cancer was notably higher in women than men included the rectum (1.3 vs. 1.0), lung (1.6 vs. 1.3), bladder (1.4 vs. 1.2), eye (1.8 vs. 1.1), and endocrine glands (2.9 vs. 1.4). The higher RR among women with second cancers of smoking-related sites, such as the lung, may be due to the lower baseline incidence rates for these cancers among females than among males, coupled with the higher frequency of cigarette smoking among cancer patients compared with the general population. Only two second cancer sites had substantially higher risks for men than for women: thyroid (2.2 vs. 1.5) and liver (1.3 vs. 1.0). The thyroid cancer difference was primarily due to the high risk observed for men within one year of diagnosis of the initial primary.

Etiologic Hypotheses

The introductory chapter on multiple primary cancers in the NCI monograph [4] discussed a number of observations previously reported in other studies. The etiologic hypotheses are listed in Table 1 and are further discussed below, emphasizing the new findings from the current investigation.

Tobacco and Alcohol Table 2 presents recent findings from Connecticut suggesting the possible influence of cigarette smoking and/or alcohol consumption on the development of both first and second cancers [5]. Figure 2 depicts the high risk of developing a new cancer of the oral cavity following a primary cancer of the lung over time and further exemplifies the continuing influence of past or current exposures on cancer risk. Tobacco smoking is clearly one of the major causes of second cancers as it is for the first cancers [6]. Previous studies of second tumors among patients with lung cancer have found excess cancers of the oral cavity, larynx, bladder, cervix, and other tobacco-related sites [3,7,8,9,10,11]. The combined effects of tobacco and alcohol account largely for the constellation of multiple cancers arising in the oral cavity, larynx, and esophagus. The risks of developing a second tobacco- or alcohol-related

TABLE 2
Examples of Observed-to-Expected Ratios of Certain Cancers for Which the First and Second Cancer Might Be Associated with Cigarette Smoking and/or Alcohol Consumption

First Cancer	Second Cancer	No. Second Cancers	RR*
Lung	Lung	110	1.5
	Oral cavity**	46	2.5
Larynx	Lung	178	3.2
	Oral cavity	40	2.7
Esophagus	Oral cavity	11	7.8

*O/E ratios for second primaries with $p < .05$
**ICD-O 140–149

cancer have been linked mainly to the habits prevailing before the onset of the initial cancer, although continued smoking and drinking may enhance the risk [10]. Clearly, it is prudent to advise patients to stop or curtail their consumption of alcohol and cigarettes.

Endocrine and Dietary Factors Table 3 presents recent findings from Connecticut confirming the significant associations previously reported for cancers of the colon, breast, uterine corpus, and ovary [12,13,14]. The bidirectional nature of these associations is remarkable. Figure 3 indicates the elevated risk of a second cancer of the female breast over time following an initial primary breast cancer. These high risks could be associated with hormonal, dietary, and/or genetic influences, as well as heightened medical surveillance. The constellation of multiple cancers of the breast, uterine corpus, ovary, and colon has long intrigued investigators [15,16,17,18,19,20].

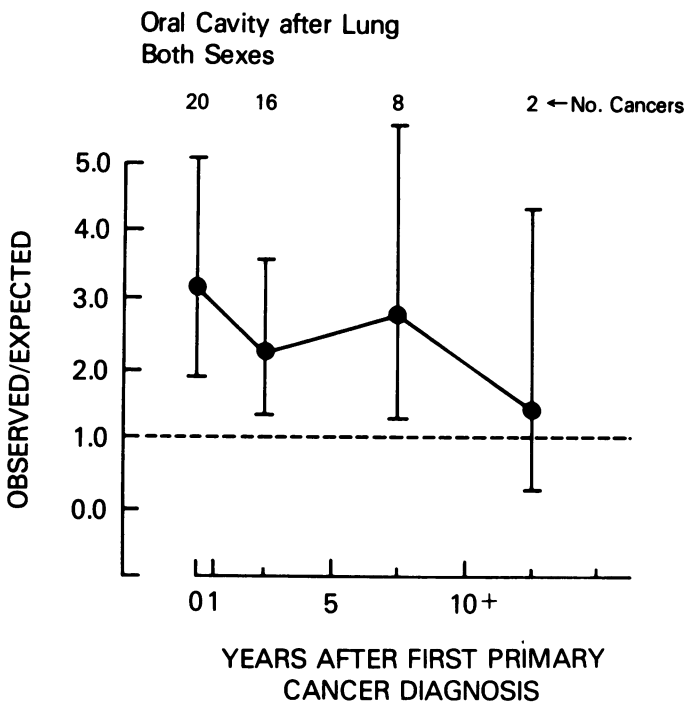

FIG. 2. Example of possible influence of an environmental factor, tobacco smoking, associated with both first and second cancer development. Observed/expected ratios for cancer of the oral cavity by time since diagnosis of an initial primary lung cancer, both sexes combined. 95 percent confidence intervals are presented.

TABLE 3
Examples of Observed-to-Expected Ratios of Certain Cancers for Which the First and Second Cancers Might Be Associated with Hormonal and/or Dietary Factors

First Cancer	Second Cancer	No. Second Cancers	RR*
Colon	Breast	232	1.2
	Uterine corpus	80	1.7
	Ovary	77	2.4
Breast	Colon	411	1.2
	Uterine corpus	227	1.4
	Ovary	183	1.7
Corpus uteri	Colon	192	1.4
	Breast	297	1.3
Ovary	Colon	63	2.0
	Uterine corpus	26	1.6
	Breast	87	1.4

*O/E ratios for second primaries with $p < .05$

Because reproductive factors (e.g., nulliparity) and dietary habits (e.g., high fat intake) appear involved in these cancers, some think that nutritional and hormonal interactions may contribute to the development of multiple primaries of these sites [21,22].

Genetic Predisposition Table 4 presents recent findings from Connecticut suggesting the possible influence of genetic predisposition on the development of some multicentric cancers and also on the high risk of osteosarcoma after retinoblastoma [2,23]. Although it is unlikely that hereditary cancers contribute substantially to the overall incidence of second tumors among cancer patients, some complexes of tumors result from genetic factors. The association between bilateral retinoblastoma and osteosarcoma illustrates the influence of hereditary factors [24]. Genetic predisposition may also contribute to multicentric cancers arising in the colon and bilateral breast cancer, which are associated with a tendency to familial aggregation. Certain

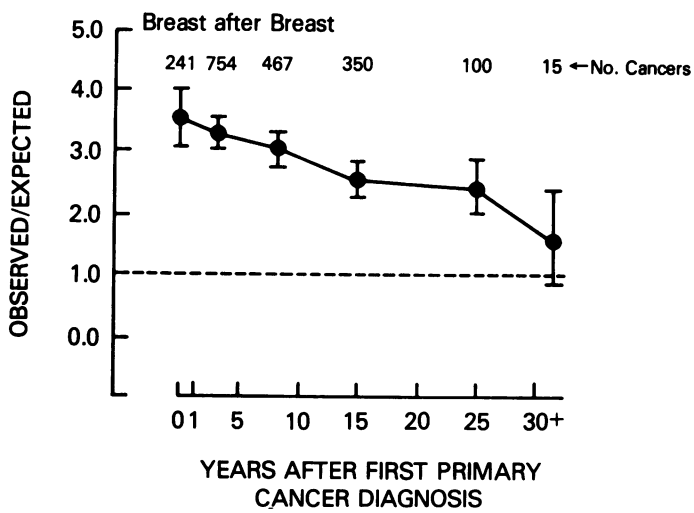

FIG. 3. Example of possible influence of hormonal, dietary, and/or genetic factors associated with the development of both first and second cancers. Observed/expected ratios for second breast cancer by time since diagnosis of an initial primary breast cancer. 95 percent confidence intervals are presented.

TABLE 4
Examples of Observed-to-Expected Ratios of Certain Second Cancers for Which the First and Second Cancers Might Be Linked Due to a Genetic Predisposition, Including the Tendency for Multicentric Tumors to Develop
(Ratios for other multifocal tumors are also listed for completeness.)

First Cancer	Second Cancer	No. Second Cancers	RR*
	Possible Genetic Predisposition		
Breast	Breast	1,927	3.0
Colon	Colon	506	2.1
Melanoma	Melanoma	30	8.5
Thyroid	Thyroid	5	4.7
Eye	Bone	3	35.7
	Other Multifocal Tumors		
Mouth	Mouth	50	25.1
Lung	Lung	110	1.5
Kidney	Kidney	16	2.9
Testis	Testis	6	11.2
Connective tissue	Connective tissue	4	6.3

*O/E ratios for second primaries with $p < .05$

families appear prone to developing cancer of diverse sites (e.g., adenocarcinomas of colon and endometrium; soft tissue sarcomas and breast cancer), with multiple primaries occurring at an early age in some family members [25]. Genetic-environmental interactions are illustrated by the high risk of radiogenic sarcomas in hereditary forms of retinoblastoma and in the cancer family syndrome described by Li and Fraumeni [26].

TABLE 5
Examples of Observed-to-Expected Ratios of Certain Cancers for Which the Second Cancer Might Be Associated with Prior Radiotherapy for the Initial Primary Cancer

First Cancer	Second Cancer	No. Second Cancers	RR*
Cervix	Kidney	11	3.4**
	Bladder	28	5.0**
	Rectum	36	3.0**
	Ovary	16	1.8**
	Breast	36	0.7
Uterine corpus	Rectum	22	2.0**
	ANLL	10	2.4
Ovary	Colon	11	2.6**
	Rectum	6	3.5**
	Bladder	6	7.2**
Breast	Lung	24	2.8**
Hodgkin's disease	Breast	8	3.0**
	Thyroid	4	6.7
	Oral cavity	7	3.1
	Lung	12	5.5**
Bone	Connective tissue	2	16.4

*O/E ratios for second primaries with $p < .05$
**10+ year survivors

TABLE 6
Examples of Observed-to-Expected Ratios for Certain Cancers for Which the Second Cancer Might Be Related to Chemotherapy for the Initial Primary Cancer

First Cancer	Second Cancer	No. Second Cancers	RR*
Multiple myeloma	ANLL	9	16.0
Ovary	ANLL	7	43.0

*O/E ratios for second primaries with $p < .05$

Multifocal Origins Other than genetic predisposition, possible reasons for the high risk associated with developing a second tumor of the same site or in contiguous tissue (Table 4) include the influence of common etiologic factors (such as cigarette smoking, diet, hormonal factors), heightened medical surveillance, and mistaken metastases. It should be noted that for paired organs such as the breast, testis, and kidney, risk estimates for developing a second tumor of the contralateral organ are likely underestimates by a factor approaching two. This is because rates from the general population are based upon persons having both paired organs intact, whereas the patients with cancer of these sites usually have the cancerous organ removed surgically and thus have only one contralateral organ at risk for subsequent cancer development.

Treatment Effects Tables 5 and 6 present recent findings from Connecticut suggesting the possible influence of radiotherapy and chemotherapy on the development of certain second cancers. The high risks of cancers of the breast, thyroid, oral cavity, and lung following Hodgkin's disease treatment (Table 5) are noteworthy since these sites can receive intense radiation exposures. Figure 4 indicates the high risk of bladder cancer possibly associated with radiotherapy for cervical cancer [14], and Fig. 5 indicates the high risk of acute non-lymphocytic-leukemia (ANLL) that appears linked to chemotherapy for ovarian cancer [2,27]. Clearly, in the absence of such

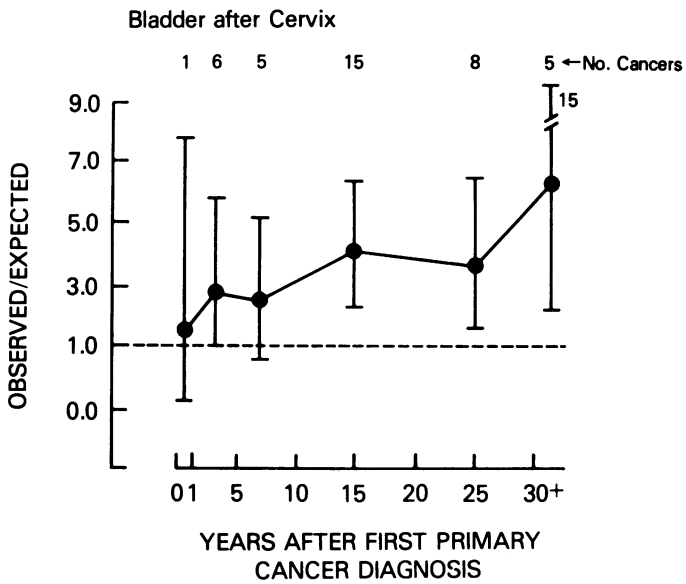

FIG. 4. Example of possible influence of radiation treatment on the development of a second cancer. Observed/expected ratios for second bladder cancer by time since diagnosis of an initial primary cervical cancer. 95 percent confidence intervals are presented.

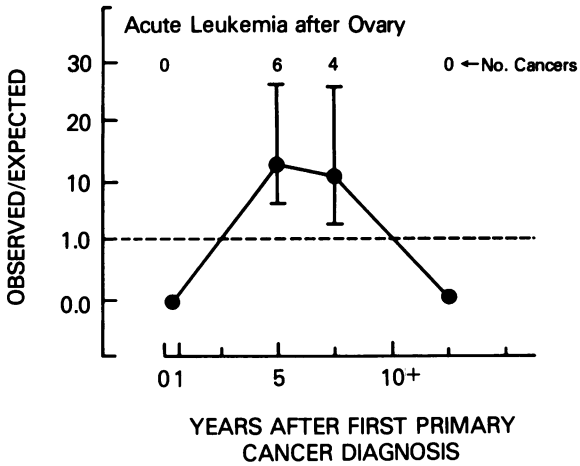

FIG. 5. Example of possible influence of chemotherapy on the development of a second cancer. Observed/expected ratios for acute non-lymphocytic leukemia by time since diagnosis of an initial primary ovarian cancer. 95 percent confidence intervals are presented.

treatment for ovarian cancer, patient survival is often dismal, but in other settings where chemotherapy is given in an adjuvant fashion, careful assessment of the risks and benefits is essential. Interestingly, ANLL was not found to be increased following Hodgkin's disease or non-Hodgkin's lymphoma (NHL). These negative findings, however, were not unexpected, since tumor registry coding practices in the past were such that ANLL would not be recorded as a separate independent second cancer when the first cancer was a malignant lymphoma [28].

During the last twenty years, the number of cancer patients treated with radiation and chemotherapy has increased, and the study of therapy-related second cancers has become more important [28,29]. Children treated with radiotherapy have been reported at high risk of second cancers [30,31], although the risk of subsequent leukemia does not seem significantly affected by radiation [32]. Cervical cancer patients exposed to high-dose radiotherapy are prone to develop cancers of the rectum and other sites within the pelvis that receive substantial radiation exposures [33]. In this group, a significantly low rate of breast cancer appears due, in large part, to a protective effect resulting from ovarian ablation. Radiotherapy increases the risk of leukemia following relatively low-dose total body irradiation for NHL [34] and of osteosarcomas following high-dose radiotherapy for Ewing's sarcoma [35] and retinoblastoma [24]. Soft tissue sarcomas also appear to be a rare consequence of high-dose

TABLE 7
Observed-to-Expected Ratios of Certain Cancers for Which the Second Cancer Might Be Related to Immunosuppression Associated with the Initial Primary Cancer and/or Treatment for the Initial Primary Cancer

First Cancer	Second Cancer	No. Second Cancers	RR*
Leukemia	Melanoma	5	3.7**
NHL	Melanoma	6	3.1**
NHL	Stomach	20	1.7

*O/E ratios for second primaries with $p < .05$
**Males only

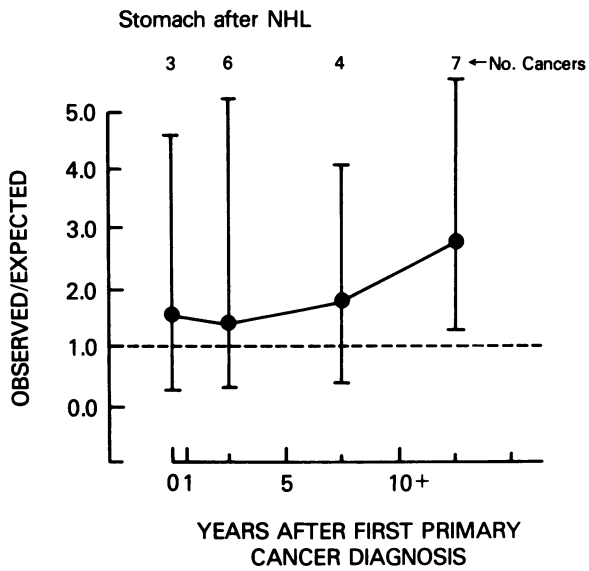

FIG. 6. Example of possible influence of immunosuppression on the development of a second cancer. Observed/expected ratios for second stomach cancer by time since diagnosis of non-Hodgkin's lymphoma (NHL), both sexes combined. 95 percent confidence intervals are presented.

radiotherapy for cancer [36]. Estrogen therapy and ovarian radiotherapy for breast cancer have both been related to an increased risk of endometrial cancer [37,38]. Alkylating agents have been associated with extremely high risks of subsequent ANLL following treatment for ovarian cancer [27], gastrointestinal cancers [39], breast cancer [40], multiple myeloma [41], lung cancer [42], Hodgkin's disease [43,44], NHL [34], and childhood cancers [31]. Cyclophosphamide, an alkylating agent, has been associated with bladder cancer as well as chronic cystitis [45].

Immunologic Defects Table 7 presents recent data from Connecticut suggesting the role of immunosuppression in the development of second skin cancers [46]. Figure 6 indicates the high risk of stomach cancer after NHL due to radiation therapy or to immunosuppression. Stomach cancer is known to complicate certain states of immunodeficiency [47,48], and the immune defects which accompany lymphoma may be aggravated by radiation or chemotherapy [49]. Certain cancers are thought to be complicated by immunodeficiency states which appear to predispose to certain cancers. For example, skin cancers (melanoma and non-melanoma) have occurred excessively after chronic lymphocytic leukemia [50]. An increase of NHL following Hodgkin's disease has been linked to the immunosuppressive effects of combination chemotherapy and radiotherapy [51]. Various cancers, in particular NHL, have occurred excessively in organ transplant recipients treated with immunosuppressants [48].

Obscure Mechanisms A number of associations between cancers have been reported without apparent explanation. For example, cancers of the breast and salivary gland have clustered in several [52,53,54] but not all studies [55,56], and leukemia has occurred excessively following cancer of the testis [3], but the mechanisms are uncertain. Table 8 presents some tumor relationships from Connecticut for which no explanation appears obvious [2]. Leukemia, for example, has been found in excess following cancers of the prostate, testis, and lip. Due to the multiple comparisons made, chance cannot be easily ruled out; however, some of the associations might provide leads for new etiologic hypotheses.

TABLE 8
Examples of Observed-to-Expected Ratios of Certain Cancers for Which a Possible Explanation Is Not Readily Available

First Cancer	Second Cancer	No. Second Cancers	RR*
Leukemia	Lung	54	2.1
	Female genital	3	0.3
Non-Hodgkin's lymphoma	Brain	9	3.1
Thyroid	Kidney	10	4.8
Eye	Lung	14	2.5
Prostate	Leukemia	64	1.3
Testis	Pancreas	6	3.9
	Leukemia	8	5.2
Breast	Multiple myeloma	14	0.5
Rectum	Stomach	34	0.7
Lip	Leukemia	17	2.1

*O/E ratios for second primaries with $p < .05$

CAUTIONS IN INTERPRETATION

The results from our analyses of multiple primary cancer must be interpreted in light of changes in medical care and reporting practices that occurred over the many years of cancer registration in Connecticut [4]. Risk factors common to multiple cancer have also varied over time, as illustrated by the increasing proportion of smokers among women in our population [57]. Intense medical surveillance and conditions peculiar to the evaluation of second cancers (e.g., misclassified metastases and autopsy diagnoses) may also affect the reported incidence of second cancers. Medical surveillance bias, for example, may have been responsible for the high rates of second cancers of the prostate, kidney, and thyroid frequently seen in Connecticut (Table 9). Interestingly, only patients with prostate cancer were at significantly low risk for second cancer development; however, this might be an artifact of case-finding, since advanced age at initial diagnosis was generally associated with an underascertainment of second cancer. The frequency of autopsies also contributes to the number of second cancers. For example, 1,280 second prostate cancers were observed overall compared to 893 expected, but 316 of the 387 excess prostate cancers were identified

TABLE 9
Examples of Observed-to-Expected Ratios for Which the Risk of Second Cancers Might Be Related to Increased (or Decreased) Medical Surveillance of Persons with an Initial Primary Cancer

First Cancer	Second Cancer	No. Second Cancers	RR*
Lung	Prostate	121	2.0
Breast	Thyroid	28	1.6
Prostate	Esophagus	15	0.5
	Stomach	61	0.7
	Colon	174	0.9
	Lung	182	0.7
	Brain	2	0.2

*O/E ratios for second primaries with $p < .05$

TABLE 10
Examples of Observed-to-Expected Ratios of Certain Cancers for Which the "Autopsy Only" Diagnoses for the Second Cancer Were Responsible in Large Part for the Significance of the Findings

First Cancer	Second Cancer	No. Second Cancers	RR*
Leukemia	Prostate	41	1.7
	Kidney	13	3.1
Bladder	Prostate	236	1.6
Kidney	Prostate	43	1.5
Kidney	Bone	3	9.0
Stomach	Kidney	12	2.2
Colon	Kidney	48	1.4
	Brain	13	1.9**
Esophagus	Thyroid	2	17.2

*O/E ratios for second primaries with $p < .05$
**Females only

only on the basis of autopsy findings or death certificate reports. For some multiple cancers such as those listed in Table 10, the autopsy diagnoses were responsible in large part for the significance of the findings. The practice of radiation therapy has also changed as supervoltage machines have replaced orthovoltage units, and different dose distributions to organs receiving scatter radiation may alter the pattern of second cancer occurrence. New therapies such as chemotherapy have been introduced and affect the risk of some second cancers, most notably ANLL [28]. Some findings might be influenced by changing coding classifications of cancer and by misclassifications of therapy in registry records. Finally, in any analysis which involves a large number of comparisons, one can expect spurious associations to develop based on chance alone.

The special advantages of this survey, however, are the exceptionally large number of subjects studied in a population-based cancer registry, the long follow-up available (almost fifty years), and the strict criteria used by a single registry to record second primary cancers. Thus, our survey of multiple primary cancers in Connecticut provides investigators with a special opportunity to estimate risks and clarify constellations of multiple cancer. A better understanding of multiple cancers should yield greater insights into the risk factors and basic mechanisms of carcinogenesis and provide a more sound basis for the management of cancer-prone individuals, including the development of protective measures.

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