

Methodologic Perspectives on the Study of Multiple Primary Cancers

W. DOUGLAS THOMPSON, Ph.D.

Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut

Received December 24, 1985

Investigations of the patterns of occurrence of multiple primary cancers of the same organ or of different organs provide important data concerning the carcinogenic potential of various therapies used in the treatment of cancer. Associations between cancers arising in different organs may also suggest hypotheses concerning shared risk factors that are strongly related to the incidence of both types of tumors. Studies of multiple primaries of a single organ permit exploration of a number of questions of etiologic interest. First, a strong same-site association over and above what would be expected on the basis of known risk factors suggests that the unexplained proportion of cancer incidence represents relatively stable characteristics of individuals rather than sporadic events. Second, detailed comparisons of risk factors for first versus second primaries of a particular site may help to identify etiologically distinct subtypes of the disease. Third, even if distinct subtypes do not exist, the study of risk factors for a second primary among those who have had a first primary of the same site may enhance the detection of the etiologic role of a particular exposure. Such detection is enhanced when the effects of the exposure are modified by some other factor that is itself a strong risk factor but that is not measured. Finally, studies of multiple primaries of a single site are of particular benefit to clinicians who must decide on appropriate levels of surveillance and preventive intervention.

Patterns of multiple primary cancer have intrigued researchers for decades [1-22]. In light of this continuing interest and the ready availability of data on multiple primaries from cancer registries around the world, it seems worthwhile to examine the nature of the inferences that can be drawn from empirical studies of multiple primary cancers. In this paper I will first consider the interpretation of associations involving two different organs and will then discuss multiple primaries of a single organ, with particular emphasis on the risk of developing contralateral breast cancer among women with a first primary breast cancer.

MULTIPLE PRIMARY CANCERS IN DIFFERENT ORGANS

Even in the absence of any systematic bias due to the effects of misclassification or other methodologic problems, a number of possible interpretations must be considered for an observed elevation in the risk of one type of primary cancer subsequent to the diagnosis of some other primary cancer. It may be that the initial cancer has some lasting effect on patients that alters their susceptibility to a new primary. Available evidence indicates that any overall increase in susceptibility seems to be modest, if in fact it exists at all. Rates for subsequent cancer of any site among those with a first

primary are only slightly elevated relative to rates in the general population [16], and part of this apparent excess may be an artifact of an increased level of surveillance for people who have had a first primary cancer.

The effects of treatment are a second possible explanation for an observed elevation in the risk of a particular cancer among those with a first primary of another site. Thus, for example, observed associations between cervical cancer and subsequent risk of cancer of the rectum [23] may reflect radiation-induced cancer as a result of the radiotherapy that is often given to patients with cervical cancer. Widespread use of chemotherapeutic agents may also account for associations between specific types of primary cancer. In general, overall examination of associations between types of cancer is not the most useful method for assessing possible carcinogenic effects of cancer therapy. More informative is a comparison of risks for second primaries among those receiving various treatment modalities for first primary cancer. Instead of comparing the risk for all persons with a given first primary to the risk in the general population, one makes comparisons within the patient group. This approach has the advantage of isolating the effects of particular modalities, whereas grouping all patients with a given primary would obscure an effect for a treatment that is given to only a subgroup of patients with the first primary cancer under investigation. This approach also has the advantage of eliminating the potential for confounding due to differences between cancer patients and the general population in terms of their levels on risk factors related to the incidence of the subsequent primary cancer under study.

Shared Risk Factors

Of potential etiologic interest is the possibility that an association between two types of primary cancer reflects a causal relationship between a risk factor and each of the two cancers. If two cancers are known to share a particular risk factor, then demonstration of an association between the two cancers in a study of multiple primaries would serve as confirmation of the etiologic role of the risk factor. Thus, for example, because of the effects of smoking, one would expect to observe an elevated risk of bladder cancer among patients with a first primary cancer of the lung. The empirical demonstration of such an association [24] confirms the etiologic role of smoking in both types of cancer. Similarly, an observed elevation in the risk of subsequent endometrial cancer among women with a first primary cancer of the breast [25,26] reflects at least in part the reproductive factors that have been shown in extensive analytic studies to be related to the incidence of both cancers [27]. Of greater interest to epidemiologists would be associations between cancers that had not previously been known to share any risk factor. In those instances, the epidemiologist may be confronted with an important new lead concerning the etiology of both types of cancer.

When attempting to assess the reasonableness of a shared risk factor as an explanation for an observed association between two types of cancer, the judgment made is usually a qualitative one. That is, if one or more risk factors are known to be related to both types of cancer, then the relationship between the cancers is regarded as having been explained. Nevertheless, a strong case can be made for a more quantitative approach to the assessment of shared risk factors.

Consider the hypothetical numerical example in Table 1. A binary risk factor is assumed to be present in 50 percent of the population. Cancer A and Cancer B are each assumed to develop in 0.1 percent of persons who do not have the risk factor and in 0.5

TABLE 1
 Example of Calculation of the Odds Ratio for the Association Between Two Cancers That Have a Risk Factor in Common

		Cancer B		
		+	-	
<i>Risk Factor Present</i>				
Cancer A	+	$\frac{(0.0025)^2}{0.5}$	$\frac{(0.0025)(0.4975)}{0.5}$	0.0025
	-	$\frac{(0.4975)(0.0025)}{0.5}$	$\frac{(0.4975)^2}{0.5}$	0.4975
		0.0025	0.4975	0.5000
<i>Risk Factor Absent</i>				
		Cancer B		
		+	-	
Cancer A	+	$\frac{(0.0005)^2}{0.5}$	$\frac{(0.0005)(0.4995)}{0.5}$	0.0005
	-	$\frac{(0.4995)(0.0005)}{0.5}$	$\frac{(0.4995)^2}{0.5}$	0.4995
		0.0005	0.4995	0.5000
<i>Total</i>				
		Cancer B		
		+	-	
Cancer B	+	0.00013	0.002987	0.003000
	-	0.002987	0.994013	0.997000
		0.003000	0.997000	1.000000
		Odds Ratio = 1.45		

percent of those who do have the risk factor, for a relative risk of 5.0. Within the two categories of the risk factor, Cancers A and B are independent, as would be the case if the shared risk factor were the only basis for the association between the two types of cancer. Thus, for example, the proportion of the population that has the risk factor and develops Cancer A but not Cancer B is $(0.0025)(0.4975)/(0.5) = 0.0024875$. At the bottom of Table 1 is given the cross-classification for Cancer A and Cancer B without regard to the shared risk factor. Note that although the risk factor increases the probability of developing each cancer fivefold, the magnitude of the resulting association between the cancers is relatively small (odds ratio = 1.45).

Table 2 gives the magnitude of corresponding odds ratios for a variety of circumstances. The relative risk for the association between the risk factor and each of the two cancers is varied from 2 to 10, and the prevalence of the risk factor in the population is varied from 5 percent to 50 percent. Table 2 illustrates that the magnitude of the association between the cancers depends in part on the prevalence of the shared risk factor and that the association between the cancers is substantial only when the shared risk factor is strongly related to both of the cancers.

These numerical results have some important implications for the study of multiple

TABLE 2
 Magnitude of the Odds Ratio for the Association Between Two Cancers
 That Have a Risk Factor in Common

Relative Risk for Cancer A	Relative Risk for Cancer B	Prevalence of Risk Factor			
		0.05	0.10	0.20	0.50
2	2	1.04	1.07	1.11	1.11
	5	1.15	1.23	1.30	1.22
	10	1.28	1.39	1.43	1.28
5	5	1.53	1.74	1.80	1.45
	10	1.99	2.23	2.15	1.55
10	10	2.85	3.04	2.68	1.68

primary cancers. They clearly indicate that it would be unlikely indeed for a study of multiple primaries to provide etiologic leads concerning subtle risk factors, the effects of which had not been detected in other types of epidemiologic studies examining the risk factors more directly. The results also suggest that a qualitative explanation in terms of a shared risk factor may not in fact be sufficient to explain the observed magnitude of association between two cancers. To assess whether additional hypotheses should be considered, prior knowledge concerning the magnitude of the association between the shared risk factor and each of the cancers and concerning the distribution of the risk factor in the population may be used to perform calculations similar to those in Table 1. The resulting value gives the strength of the association that would be anticipated if the shared risk factor were the only basis for a relationship between the two cancers. Comparison of this value to the observed strength of the association between the two cancers based on registry data indicates whether additional explanations for the association between the cancers should be considered.

Correlated Risk Factors

In a recent study of multiple primary cancer in Finland, the authors stress that an association between two cancers may be induced by two risk factors that are not shared by the cancers but that tend to be found more frequently in certain subgroups of the population [24]. For example, they postulate that a negative association between smoking-related cancers and cancer of the colon is attributable to the relatively high prevalence of smoking and the relatively low prevalence of risk factors for cancer of the colon in the lower socioeconomic classes in Finland. Figure 1 illustrates the distinction between shared risk factors and correlated risk factors.

As a guide to assessing the likely magnitude of association between two cancers as a result of correlated risk factors, numerical results are presented in Table 3. The magnitude of the relative risk for one risk factor as it relates to Cancer A is varied from 2 to 10, as is the relative risk for a different risk factor as it relates to Cancer B. The prevalences for the two risk factors are assumed to be equal in the total population, and this value is varied from 5 percent to 50 percent. The correlation between the risk factors in the population is assumed to be fairly substantial throughout. Specifically, it is assumed that in half of the population (e.g., those below the median on socioeconomic status) the prevalence of each of the risk factors is four times greater than in the other half of the population (e.g., those above the median on socioeconomic status). For risk factors having a prevalence of 50 percent overall, this degree of correlation

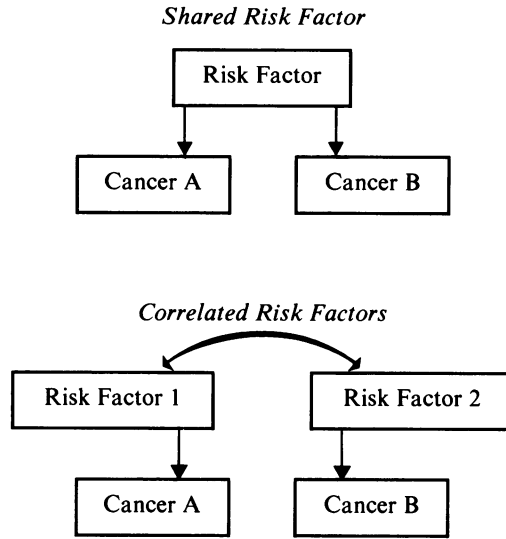


FIG. 1. Shared Versus Correlated Risk Factors in Multiple Primary Cancers *Note:* Straight arrows indicate causal relationships, whereas the curved double-headed arrow indicates a statistical association that is not causal. For both shared and correlated risk factors, an association is induced between Cancer A and Cancer B.

between the risk factors corresponds to a prevalence of 80 percent for each of the risk factors in one half of the population and a prevalence of 20 percent for each in the other half.

As would be expected, correlated risk factors related etiologically to different cancers induce less of an association between the two cancers than does a single risk factor that is etiologically related to both. The results in Table 3 indicate further that the association induced by correlated risk factors is generally of extremely small magnitude. Only when both of the risk factors are strongly related to their respective cancers is the association large enough to render correlated risk factors a plausible explanation of substantial observed associations between pairs of cancers. This general

TABLE 3
Magnitude of the Odds Ratio for the Association Between Two Cancers for Which Risk Factors Are Correlated in the Population^a

Relative Risk for Factor 1 and Cancer A	Relative Risk for Factor 2 and Cancer B	Prevalence of Factor 1 and of Factor 2			
		0.05	0.10	0.20	0.50
2	2	1.00	1.00	1.01	1.04
	5	1.00	1.01	1.03	1.08
	10	1.01	1.02	1.04	1.10
5	5	1.01	1.03	1.07	1.16
	10	1.02	1.05	1.10	1.20
10	10	1.03	1.08	1.15	1.24

^aIt is assumed that in one half of the population the prevalence of Factor 1 and the prevalence of Factor 2 are each four times as great as in the other half of the population (e.g., prevalence of 0.20 in one half and 0.80 in the other).

lack of impact of correlated risk factors on patterns of multiple primary cancers is probably fortunate from the point of view of inferences concerning etiology. Thus, when assessing the possible role of risk factors as an explanation for an observed association between two types of cancer, it is not generally necessary to consider separate risk factors that may happen to be correlated in the population. The researcher can concentrate on the more manageable task of attempting to identify a risk factor that the two cancers might share.

MULTIPLE PRIMARY CANCERS OF THE SAME ORGAN

Provided that the entirety of an organ in which a first primary cancer has arisen is not removed during the course of therapy, the possibility exists for the occurrence of a second primary of that same organ. When studying multiple primaries of a single site, there are two general types of comparisons that can be made. The first type involves comparisons between those with a first primary cancer of a particular organ and persons in the general population. These groups are compared in terms of risk for a subsequent primary cancer of that same organ. The second type involves comparisons of subgroups of those with a first primary cancer of a particular organ. The subgroups are compared in terms of the magnitude of risk for subsequent development of a primary of that same organ.

Comparisons Between Those with a First Primary and the General Population

A number of studies have examined whether, relative to women in the general population, women who have had a first primary cancer of the breast are at an elevated risk for the development of a subsequent primary breast cancer [16,28–34]. These studies have found a substantial elevation in risk, particularly among women whose first primary breast cancer was diagnosed at an early age. Such information on the predictive utility of first primary breast cancer as a risk indicator for subsequent primary breast cancer in the contralateral breast has important clinical implications concerning appropriate levels of surveillance of various segments of the female population. Wide excisional biopsy and even prophylactic removal of the contralateral breast have been considered by some physicians as appropriate for certain women with a first primary breast cancer [35–37].

When considering multiple primaries of the same organ, the repeated effects of known risk factors for a first primary cancer are likely to account for at least some of the observed association between first primary cancer and subsequent risk for the disease. On average, for example, women with a first primary breast cancer have higher values on established risk factors for the disease than do women who have not developed the disease. A question of both clinical and etiologic interest would be whether a first primary breast cancer has any predictive utility over and above its serving as an indicator of elevated values on established risk factors for breast cancer. From a clinical perspective, if it were shown that first primary breast cancer had no predictive utility beyond what is tapped by established risk factors for breast cancer, then the clinician should select appropriate levels of surveillance on the basis of a woman's profile on established risk factors rather than on the basis of whether or not she has a history of first primary breast cancer. Thus, a woman with a first primary breast cancer but low values on the established risk factors would have the same risk for a subsequent breast primary as a woman with a similar risk factor profile but no first primary breast cancer.

From an etiologic perspective, an assessment of whether first primary breast cancer has predictive utility beyond established risk factors would possibly shed light on the nature of the currently unexplained portion of the variation in risk for breast cancer. If first primary breast cancer were shown to have no predictive utility after consideration of established risk factors, then the currently unexplained variation in risk would be more reasonably attributed to promotional agents to which one's exposure varies greatly over time than to agents involved in the early stages of carcinogenesis, to chronic patterns of exposure, or to stable characteristics of the individual.

Special studies to examine directly whether first primary breast cancer has predictive utility beyond established risk factors would be costly to mount. Prospective studies of this issue require the inclusion of large numbers of women with and without a first primary, collection of data on established risk factors, and long-term follow-up for the incidence of subsequent primary cancers of the breast. In the analysis of such a study, one would control for the established risk factors to assess whether the group with a first primary had an independent increment in risk. Case-control studies of this issue would also be rather costly in that a history of prior primary breast cancer is not an exposure factor of high prevalence, necessitating a fairly large sample size.

Fortunately, indirect methods may also be used to evaluate whether first primary breast cancer has additional predictive utility over and above the established risk factors. Available data from case-control studies of first primary breast cancer can be used for this purpose. These studies involve comparison of cases having a first primary cancer to controls from the general population and can be used to obtain logistic regression equations for the prediction of case-control status [38,39]. To determine how much higher first primary breast cancer patients are than population controls in terms of their values on established risk factors for first primary breast cancer, the mean predicted probability of being in the case group may be calculated for cases and controls separately, using the logistic regression equation.

For illustrative purposes, this approach has been applied to 889 first primary breast cancer patients and 878 population controls from a population-based case-control study conducted in Connecticut. This study was part of a larger collaborative study of oral contraceptives and breast cancer in women between the ages of 20 and 54 [40]. A logistic regression equation was fitted to the data, using as predictors the established risk factors of parity, menopausal status, age at menarche, age at first birth, age at menopause, obesity, family history of breast cancer, and history of benign breast biopsy. Information on diet was not collected. Application of the logistic equation to each member of the case group yielded an average *predicted* probability of 0.528 for being a case. The corresponding calculation for controls yielded an average predicted probability of 0.478. Although these data do not bear directly on the issue of second primary cancer, they may be used to estimate the magnitude of association between first and subsequent primary breast cancer that one would anticipate observing if first primary breast cancer had no predictive utility beyond the established risk factors for the disease. Comparison of the predicted probabilities for cases and controls from the Connecticut study yields an odds ratio of $[0.528/(1 - 0.528)]/[0.478/(1 - 0.478)] = 1.22$. That is, if established risk factors for first primary breast cancer have similar quantitative effects on the incidence of second primary breast cancer, then the elevated values of these risk factors among women with a first primary breast cancer would alone be expected to increase their risk of subsequent breast cancer 22 percent above that of women without a first primary breast cancer. Comparison of this value of 1.22

to the substantial association between first primary breast cancer and risk of subsequent breast cancer found in a number of studies of multiple primaries indicates that first primary breast cancer has substantial predictive utility over and above the established risk factors included in the logistic regression equation. Therefore, first primary breast cancer is an important independent risk factor that clinicians should continue to consider in deciding on appropriate levels of surveillance. These results also indicate that the as yet unidentified risk factors for breast cancer are unlikely to be exclusively promotional factors to which levels of exposure vary widely over time for given individuals.

Similar applications of logistic regression can be used for evaluations of whether cancers of different sites are correlated more strongly than would be expected on the basis of a number of shared risk factors. For example, the same logistic function for discriminating first primary breast cancer cases from controls may be used to estimate the expected excess of subsequent breast cancer among women with a first primary endometrial cancer. Application of the logistic regression equation from the study of breast cancer to groups of endometrial cancer cases and controls would yield the magnitude of association between primaries of the endometrium and breast that would be anticipated on the basis only of shared risk factors included in the equation.

Comparisons Among Subgroups of Those Who Have Had a First Primary

The occurrence of a first primary cancer of a particular organ defines a subgroup of the population of special interest in terms of subsequent primary cancer of that same organ. For example, among women with a first primary cancer of the breast, only a minority of those surviving the initial disease develop a second primary cancer in the contralateral breast [35]. Identification of factors related to risk of second primary breast cancer among those with a first primary breast cancer would be of both clinical and etiologic interest. Relevant risk factors for study are those known or suspected to be related to first primary breast cancer and those having to do with the characteristics of the first cancer itself. This latter group includes histologic type, extent of disease, hormone receptor status, and mode of treatment.

Both cohort and case-control studies of these issues have been conducted. For example, Hankey et al. [32] conducted a cohort study of first primary breast cancers in the Connecticut Tumor Registry and compared those treated with surgery plus radiation to those treated with surgery only in order to assess the possible role of radiation treatment in the etiology of second primary breast cancer. Hislop et al. [41] used a case-control approach and compared women developing a second primary breast cancer to a control group of women who had had a first primary breast cancer but not a second. Lobular histology for the first primary, absence of nodal involvement at time of diagnosis of the first primary, and family history of cancer were found to differ between cases and controls.

To the extent that certain risk factors may be found in future studies to have quantitatively or especially qualitatively different effects on second primary breast cancer than they have on first primary breast cancer, somewhat different disease processes may be postulated. However, even if second primary breast cancer is not etiologically distinct from first primary cancer, the study of second primary breast cancer nevertheless provides a potentially powerful means for detecting the etiologic role of certain risk factors for breast cancer in general. Some such risk factors might be virtually impossible to study in the context of first primary breast cancer.

TABLE 4
 Example of the Relationship to First Primary Cancer for a Measured Risk Factor That Is Modified by an Unmeasured Risk Factor

		First Primary Cancer			
		+	-		Risk
<i>Unmeasured Risk Factor Present</i>					
Measured Risk Factor	+	0.004	0.001	0.005	0.800
	-	0.001	0.004	0.005	0.200
		0.005	0.005	0.010	
<i>Unmeasured Risk Factor Absent</i>					
		First Primary Cancer			
		+	-		Risk
Measured Risk Factor	+	0.010	0.485	0.495	0.020
	-	0.010	0.485	0.495	0.020
		0.020	0.970	0.990	
<i>Total</i>					
		First Primary Cancer			
		+	-		
Measured Risk Factor	+	0.014	0.486	0.500	
	-	0.011	0.489	0.500	
		0.025	0.975	1.000	
Odds Ratio = 1.28					

Table 4 gives a hypothetical numerical example illustrating one type of situation in which the study of second primary cancer would be particularly advantageous. In Table 4, two different risk factors are considered. One risk factor is of low prevalence (here assumed to be 1 percent), and it either cannot be measured with currently available techniques or simply has not been considered as a possible etiologic factor. The other risk factor has been measured and is a strong risk factor for first primary cancer only among persons who have the unmeasured risk factor (assumed risks of 0.80 versus 0.20 for first primary cancer within the subgroup having the unmeasured risk factor). Within the large subgroup without the unmeasured risk factor, the risk of first primary cancer is 0.02 regardless of whether the measured risk factor is present or absent. In a study of the incidence of first primary cancer, the observed association between the measured risk factor and the disease would be as given in the cross-classification at the bottom of the table. The odds ratio for this association is 1.28, which would be extremely difficult to detect in either a cohort study or case-control study.

Table 5 illustrates the advantage of studying the same measured risk factor in the context of second primary cancer. In this table the study group is composed of those with a first primary cancer. Note that whereas persons with the unmeasured risk factor comprise only 1 percent of the total in Table 4, such persons comprise 20 percent of the

TABLE 5
 Example of the Relationship to Second Primary Cancer for a Measured Risk Factor That Is Modified by an Unmeasured Risk Factor

		Second Primary Cancer			
		+	-	Risk	
<i>Unmeasured Risk Factor Present</i>					
Measured Risk Factor	+	0.128	0.032	0.160	0.800
	-	0.008	0.032	0.040	0.200
		0.136	0.064	0.200	
<i>Unmeasured Risk Factor Absent</i>					
		Second Primary Cancer		Risk	
		+	-		
Measured Risk Factor	+	0.008	0.032	0.400	0.020
	-	0.008	0.032	0.400	0.020
		0.016	0.784	0.800	
<hr/> <i>Total</i>					
		Second Primary Cancer			
		+	-		
Measured Risk Factor	+	0.136	0.424	0.560	
	-	0.016	0.424	0.440	
		0.152	0.848	1.000	
		Odds Ratio = 8.50			

total in Table 5. In Table 5 it is assumed that the etiologic relationships of the two risk factors to second primary cancer are the same as their relationships to first primary cancer. Specifically, among those with the unmeasured risk factor there is a risk for second primary cancer of 0.80 and 0.20 for those with and without the measured risk factor, and among those without the unmeasured risk factor there is a risk of 0.02, regardless of whether the measured risk factor is present or absent. The cross-classification at the bottom of the table indicates that the observed association between the measured risk factor and the disease would be substantial in a study of second primary cancer (odds ratio = 8.5). Such an association could be detected in even a small case-control study of second primary cancer.

The example given in Tables 4 and 5 implies that certain measured risk factors that have not proved important in studies of first primary breast cancer may be masked because of the low prevalence of an unmeasured risk factor which modifies their effects. Consequently, although use of oral contraceptives seems not to be related to risk of breast cancer even in large case-control studies of first primaries [40,42], studies of second primary breast cancer might change the picture considerably.

Demonstration of etiologic relationships for second primary breast cancer that have not been detectable in studies of first primary breast cancer would contribute primarily to an understanding of the disease process. Because the enhanced detection of etiologic relationships for measured risk factors in studies of second primary breast cancer depends on potentiation by an unmeasured factor of low prevalence, the proportion of all breast cancer attributable to such measured risk factors will be small in the population. However, the new insights into etiology may hold long-term benefit for all women.

COMMENT

The existence of many long-term cancer registries throughout the world offers rich opportunities for the study of multiple primary cancers. Close scrutiny of multiple primary cancers serves the dual purpose of enlarging our understanding of cancer and ensuring the quality of data in the registries. As this methodologic review illustrates, many aspects of research on multiple primary cancer require additional information that is not routinely collected by cancer registries. Nevertheless, even for special studies involving abstraction of medical records and possible interviews of patients, cancer registries form the cornerstone in terms of the identification of persons for study.

REFERENCES

1. Warren S, Gates O: Multiple primary malignant tumors: A survey of the literature and statistical study. *Am J Cancer* 16:1358-1414, 1932
2. Lombard HL, Warren S: Association of other malignant tumors with cancer of the skin. *Am J Public Health* 35:533-536, 1943
3. Warren S, Ehrenreich T: Multiple primary malignant tumors and susceptibility to cancer. *Cancer Res* 4:554-570, 1944
4. Lombard HL, Levin ML, Warren S: Multiple malignant growths. *Cancer Res* 6:436-440, 1946
5. Watson TA: Incidence of multiple cancer. *Cancer* 6:365-371, 1953
6. Bailar JC III: The incidence of independent tumors among uterine cancer patients. *Cancer* 16:842-853, 1963
7. Einhorn J, Jakobsson P: Multiple primary malignant tumors. *Cancer* 17:1437-1444, 1964
8. Moertel CG: Multiple Primary Malignant Neoplasms: Their Incidence and Significance. New York, Springer-Verlag, 1966
9. Hajdu SI, Hajdu EO: Multiple primary malignant tumors. *J Am Geriatr Soc* 16:16-26, 1968
10. Schoenberg BS, Greenberg RA, Eisenberg H: Occurrence of certain multiple primary cancers in females. *JNCI* 43:15-32, 1969
11. Berg JW, Schottenfeld D, Ritter F: Incidence of multiple primary cancers. III. Cancers of the respiratory and upper digestive system as multiple primary cancers. *JNCI* 44:263-274, 1970
12. McCredie JA, Inch WR, Alderson M: Consecutive primary carcinomas of the breast. *Cancer* 35:1472-1477, 1975
13. Hoover R, Fraumeni JF Jr, Everson R, et al: Cancer of the uterine corpus after hormonal treatment for breast cancer. *Lancet* i:885-887, 1976
14. Penn I: Second malignant neoplasms associated with immunosuppressive medications. *Cancer* 37:1024-1032, 1976
15. Rosner F: Acute leukemia as a delayed consequence of cancer chemotherapy. *Cancer* 37:1033-1036, 1976
16. Schoenberg BS: Multiple Primary Malignant Neoplasms: The Connecticut Experience 1935-1964. New York, Springer-Verlag, 1977
17. Greene MH, Hoover RN, Fraumeni JF Jr: Subsequent cancer in patients with chronic lymphocytic leukemia: a possible immunologic mechanism. *JNCI* 61:337-340, 1978
18. Prior P, Waterhouse JA: Multiple primary cancers of the breast and ovary. *Br J Cancer* 44:628-636, 1981

19. Miké V, Meadows AT, D'Angio GJ: Incidence of second malignant neoplasms in children: Results of an international study. *Lancet* ii:1326–1330, 1982
20. Curtis RE, Hankey BF, Myers MH, et al: Risk of leukemia associated with the first course of cancer treatment: An analysis of the Surveillance, Epidemiology, and End Results Program experience. *JNCI* 72:531–544, 1984
21. Adami H-O, Bergkvist L, Krusemo U, et al: Breast cancer as a risk factor for other primary malignant diseases. A nationwide cohort study. *JNCI* 73:1049–1055, 1984
22. Schenker JG, Levinsky R, Ohel G: Multiple primary malignant neoplasms of breast cancer patients in Israel. *Cancer* 54:145–150, 1984
23. Boice JD Jr, Day NE, Andersen A, et al: Cancer risk following radiotherapy of cervical cancer: A preliminary report. In *Radiation Carcinogenesis: Epidemiology and Biological Significance*. New York, Raven Press, 1984
24. Teppo L, Pukkala E, Saxén E, et al: Multiple cancer—an epidemiologic exercise in Finland. *JNCI* 75:207–217, 1985
25. MacMahon B, Austin JH: Association of carcinomas of the breast and corpus uteri. *Cancer* 23:275–280, 1969
26. Schottenfeld D, Berg J: Incidence of multiple primary cancers. IV. Cancer of the female breast and genital organs. *JNCI* 46:161–170, 1971
27. Kelsey JL, Hildreth NG: *Breast and Gynecologic Cancer Epidemiology*. Boca Raton, Florida, CRC Press, 1983
28. Prior P, Waterhouse JAH: Incidence of bilateral tumors in a population-based series of breast cancer patients. I. Two approaches to an epidemiological analysis. *Br J Cancer* 37:620–634, 1978
29. Newell GR, Rawlings W, Krementz ET, et al: Multiple primary neoplasms in blacks compared to whites. III. Initial cancers of the female breast and uterus. *JNCI* 53:369–373, 1974
30. Schottenfeld D, Berg JW: Epidemiology of multiple primary cancers. In *Cancer Epidemiology and Prevention: Current Concepts*. Edited by D Schottenfeld. Springfield, Charles C Thomas, 1975
31. Robbins GF, Berg JW: Bilateral primary breast cancers: A prospective clinico-pathological study. *Cancer* 17:1501–1527, 1964
32. Hankey BF, Curtis RE, Naughton MD, et al: A retrospective cohort analysis of second breast cancer risk for primary breast cancer patients with an assessment of the effect of radiation therapy. *JNCI* 70:797–804, 1983
33. Newell GR: Multiple primary cancers: Suggested etiologic implications. *Cancer Bulletin* 32:160–164, 1980
34. Leis HP, Mersheimer WL, Black MM, et al: The second breast. *NY J Med* 65:2460–2468, 1965
35. Urban JA, Papachristou D, Taylor J: Bilateral breast cancer: biopsy of the opposite breast. *Cancer* 40:1968–1973, 1977
36. Hubbard TB: Nonsimultaneous bilateral carcinoma of the breast. *Surgery* 34:706–723, 1953
37. Farrow JH: Bilateral mammary cancer. *Cancer* 9:1182–1188, 1956
38. Breslow NE, Day NE: *Statistical Methods in Cancer Research. Volume 1. The Analysis of Case-Control Studies*. IARC Scientific Publication Number 32. Lyon, France, International Agency for Research on Cancer, 1980
39. Schlesselman JJ: *Case-Control Studies: Design, Conduct, Analysis*. New York, Oxford University Press, 1982
40. The Centers for Disease Control Cancer and Steroid Hormone Study: Long-term oral contraceptive use and the risk of breast cancer. *JAMA* 249:1591–1595, 1983
41. Hislop TG, Elwood JM, Coldman AJ, et al: Second primary cancers of the breast: Incidence and risk factors. *Br J Cancer* 49:79–85, 1984
42. Stadel BV, Rubin GL, Webster LA, et al: Oral contraceptives and breast cancer in young women. *Lancet* ii:970–973, 1985