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Multiple Primary Malignant Neoplasms

The Connecticut Experience, 1935-1964

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With 139 Tables

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Fortschritte der Krebsforschung
Progrès dans les recherches sur le cancer

Dedicated to the memory of

Charles Schoenberg	Louis Brodsky
Joseph Lieberman	Oliver Ross
Henry Eisenberg	Barbara Christine

and the all too many who annually succumb to cancer

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Preface

When asked why he robbed banks, an astute and successful criminal is said to have replied "Because that's where the money is kept."

Why study patients with multiple primary cancers? The answer follows the same practical approach. Because the intensive investigation of such patients is very likely to yield data useful to both the clinical and research oncologist.

Studies of this problem provide an immediate return for the clinician responsible for the care of cancer patients. With improved forms of therapy, these individuals are enjoying longer periods of survival. One important factor in maintaining increased survival is the early detection and treatment of new primary tumors which may develop. Analyses of multiple primary malignancies serve as a guide to the probable anatomic location of a subsequent primary and help define characteristics of the individual at high risk for multiple primary cancer. But just as treatment may improve the life of the cancer patient, it may also increase the risk of a subsequent malignancy. Studies of multiple primaries provide an efficient means for quantifying potentially harmful effects of current therapeutic modalities.

The present study allows one to compare the observed and expected number of subsequent primary cancers. Tumors which occur together more often than expected may reflect a common etiology. Patients with more than one malignant neoplasm deserve careful study, as this occurrence may derive from an unusually high exposure to carcinogenic factors or unusually high susceptibility to such factors. The results of this study should mirror the findings of genetic, clinical, and laboratory endeavors in research oncology.

The tabulations presented in this monograph represent the *first and only* currently available systematic review of the multiple primary cancer experience of a large-

scale, population-based tumor registry. Both the incidence rates used to calculate the expected numbers of subsequent cancers and the cohort of individuals under observation with a first primary cancer are derived from the same population. The Connecticut Registry has served as a high-quality data resource for over thirty years and is regarded as a model for cancer registration systems throughout the United States and abroad.

To carry out this investigation, the routine data collection and editing methods of the registry were supplemented by special efforts. This required a considerable investment of time and money and necessitated limiting the study to the period 1935—1964. Wherever possible, in order to reduce the chance of error, computer-generated tables were prepared in a format suitable for offset printing. Each chapter was written as a discrete unit, and although this procedure resulted in some duplication, the reader interested in particular forms of cancer can focus his attention on specific sections of the text without the need to scan the entire book. The interpretations in each chapter represent one opinion. In all cases, the results underlying these interpretations are provided. The reader is encouraged to form his own conclusions, based on these tabulations. Chapter 5 which discusses sources of bias in these analyses should be reviewed by anyone using these data. Finally, results of this investigation should not be interpreted as providing definitive answers, but rather should be regarded as stimuli to more intensive clinical, pathologic, and laboratory investigations. Only if these stimuli evoke appropriate investigative responses will this effort be considered a success.

Rochester, Minnesota

BRUCE S. SCHOENBERG

Contents

Chapter 1

Historical Background

In 1802, as members of the Society for Investigating the Nature and Cure of Cancer, a group of eight physicians and surgeons formulated a list of 13 questions to serve as a basis of further inquiry into the nature of malignant neoplasms (SCHOENBERG, 1975). One of these 13 queries addressed the issue of whether "... the existence of cancer in one part afford(s) a presumption that there is a tendency to a similar morbid alteration in other parts of the animal system." Their question was followed by reference to several anecdotal accounts of cancer involving both the breast and uterus (MEDICAL COMMITTEE OF THE SOCIETY FOR INVESTIGATING THE NATURE AND CURE OF CANCER, 1806).

John PEARSON, a surgical member of the Society had, some 9 years earlier, published a case report of cancer involving one breast, then the second breast, and finally the uterus (PEARSON, 1973). Such descriptions, although unusual, began to appear in the medical literature of the nineteenth century. There was still considerable confusion as to whether such cases represented examples of widespread metastases or rather instances of primary independent neoplasms.

BILLROTH, the first individual to establish a set of rigid criteria useful in defining the phenomenon of multiple primary neoplasms, provided a firm scientific basis for further descriptive studies. He wrote: "1) Each tumor must have an independent histologic appearance; 2) the tumor must arise in different situations; (and) 3) each tumor must produce its own metastases" (HANLON, 1931). These criteria were extremely restrictive and consequently were largely ignored by most medical writers. GOETZE in 1913 proposed a minor modification of these rules: "1) The macroscopic and microscopic appearance of the tumor must be that of the usual carcinomas of the organs involved; 2) the exclusion of metastases must be certain; (and) 3) diagnosis may be confirmed by the character of the metastases in each case" (HANLON, 1931).

In 1932, WARREN and GATES offered a set of definitions of multiple primary malignancies that have been widely adopted by other authors with little or no change. They wrote: "Each of the tumors must present a definite picture of malignancy, each must be distinct, and the probability of one being a metastasis of the other must be excluded." Four years later, BURKE (1936) adopted these same criteria. As an addendum to these rules, several authors have remarked on the necessity to exclude tumors with a known tendency to multicentric origin (AUSTIN, 1938; TULLIS, 1942). Despite the considerable effort that has been devoted to establishing such rigid criteria, some authors never specifically state the rules, if any, by which they decide whether a given cancerous lesion is indeed a second primary malignancy.

The early case reports were followed by series of cases based on the experience of individual surgeons, pathologists, or medical institutions.

While providing valuable clinical or pathologic descriptions, these data did not necessarily reflect an accurate picture of the occurrence of multiple primary cancer in a well-defined population. In order to generalize from the results of any such study, one must know the characteristics of the population yielding the specific statistics. It should also be emphasized that several case reports of two or more neoplasms occurring within the same individual do not constitute proof of a significant biologic association. The two tumors must be shown to occur together more frequently than might be expected on the basis of chance. Despite these problems, early investigations of multiple primary malignancies were useful in defining and documenting the phenomenon.

Finally, a number of case-control comparisons were carried out. Such investigations were based on the assumption that the cases under consideration were representative of all such cases, and that the controls were representative of the general population. Unfortunately, the validity of this assumption was unknown. In many instances, authors attempted to use rough estimates of cancer incidence in the general population as the comparison against which to judge data concerning multiple primary malignancies. The problem of developing suitable statistical methods became critical, for it was necessary to predict whether the occurrence of multiple primary neoplasms together in the same individual was simply the result of chance. At first, many authors merely gave their opinion on the matter, not relying on any accepted tests of statistical significance. In 1938, after being challenged on the validity of his statistical methods, AUSTIN replied: "Perhaps I overstated the case; a number of articles have attempted statistical analysis, comparing the population and cancer incidence, and multiple cancers seem to occur more often than chance would indicate. It is probable that this is significant, although I do not think it has been mathematically proved" (AUSTIN, 1938).

In 1934, BUGHER derived an equation for the probability of death from cancer during a given age span with a coincidental second malignancy. In the development of his analytic method he assumed "... that the mortality function may be used as a morbidity function without great error ... (and that) the error introduced by such an assumption is probably no greater than the intrinsic inaccuracy of the mortality data."

PELLER (1941) reasoned that since fewer than 20% of people over age 40 develop cancer, for about four-fifths of the population over age 40, the cancer risk is practically zero. He therefore believed that cancer susceptibility for the remaining one-fifth of the population in this age group is at least five times that indicated by data derived from the average population. Using this inflated rate for "cancer susceptibles," he concluded that a first skin cancer protected against the development of a possible new internal malignancy. Unfortunately, PELLER was unable to identify the "susceptible" fraction of the population. As noted by EPSTEIN (1954), PELLER could not "... state with certainty that a larger percentage would not develop cancer if they did not die of other causes."

In order to determine the number of observed and expected second primary cancers, LOMBARD et al. (1946) obtained expected values "... by multiplying person-years (of observation) by the age-sex-site specific incidence rate and reduced (these figures) when necessary by (appropriate) correction factors...." WATSON in 1953 used similar techniques.

Despite these elaborate methods and the large volume of data collected, studies were still inadequate in many respects. In 1961, MOERTEL et al. criticized the state of analyses of this subject up to that time. They wrote: "On the whole, the literature concerning this subject leaves the impression that the incidence of a second cancer of a different organ

or tissue in patients whose first lesion has been treated successfully is probably equal to, and perhaps exceeds, that in the general population. However, convincing statistical evidence is still lacking, and because the establishment of an entirely adequate control group seems impossible at this time, no attempt at this type of analysis will be made in the present study."

IMPORTANCE OF TUMOR REGISTRIES

The formation of tumor registries and the resulting implementation of efficient follow-up procedures greatly aided in identifying a sufficient number of individuals with multiple primary malignancies and greatly facilitated case-control studies of this phenomenon. A number of reports have been published based on the multiple primary cancer experience of the Memorial Hospital for Cancer and Allied Diseases in New York (ROBBINS and BERG, 1964; BERG, 1967, BERG et al., 1968; SCHOTTENFELD et al., 1969; BERG et al., 1970; SCHOTTENFELD and BERG, 1971; SCHOTTENFELD et al., 1974), and Charity Hospital in New Orleans (NEWELL et al., 1974a; NEWELL et al., 1974b; NEWELL et al., 1974c; NEWELL et al., 1975). Unfortunately, the underlying population from which these hospitals draw patients is not well-defined. This leads to difficulties in choosing an adequate control population with which to compare the results of the tumor registry tabulations.

The most sophisticated studies of multiple primaries have been based on data from well-defined population groups. A population-based tumor registry is ideal for such an analysis, particularly if it has a large, well-defined group under observation for a period of 10 or more years. The optimal methodology for this type of investigation is one which makes it possible to compare the observed and the expected number of subsequent primary malignancies. This is most conveniently done through a person-years approach. Such a procedure adjusts for the age and sex distribution as well as for the survival experience of patients with a first primary cancer. Details of this method and the rationale for its use are described in Chapter 2. It is best if the incidence rates used in this procedure are derived from the same population yielding the first primary malignancies. A population-based tumor registry fulfills this condition. Otherwise, differences between the observed and expected number of subsequent primaries might be attributable to differences in the characteristics between the population yielding the incidence rates and the population to which the rates are applied.

Such a person-years approach makes it possible to determine whether an individual with a malignancy in a particular organ or tissue has an increased, decreased, or unchanged risk of developing a later primary malignancy in the same or another organ or tissue. If the patient with one cancer had a decreased chance of developing a new malignancy, it may be that the presence of the first tumor in some way protected the individual; studies of the mechanism of such protection might be useful. If, on the other hand, one cancer placed the patient at higher risk for a subsequent primary malignancy, it may be that the same oncogenic factors are operating in the pathogenesis of both neoplasms. Such analyses are useful in identifying the high-risk cancer patient. It is these individuals who deserve further study with respect to possible etiologic factors.

CONNECTICUT EXPERIENCE

Using the data resources of one such population-based tumor registry, GREENBERG (1959b) and BAILAR (1963) accumulated experience in terms of person-years of observation and used incidence rates from the same population yielding the first primary cancers. They now had an adequate control - made possible by the unique capabilities of the Connecticut Tumor Registry.

The Connecticut Tumor Registry, begun in 1941, maintains records on all Connecticut patients with a diagnosis of malignant neoplasm admitted to a hospital in the state or who have such a diagnosis on their death certificate. In addition, the registry routinely receives reports on Connecticut residents with a diagnosis of cancer seen at major referral centers in neighboring states. Data were also obtained retrospectively through 1935. An attempt is made to follow all patients from diagnosis to death, and it is estimated that fewer than 5% of the cases are lost to follow-up (GREENBERG, 1959b). In certain instances (e.g., intracranial tumors), benign neoplasms are also reportable to the registry. Information received from hospitals, physicians, and death certificates are coded according to a uniform format (END RESULTS SECTION, NATIONAL CANCER INSTITUTE, 1967), and the coded tabulations are placed on magnetic tape. The Connecticut Tumor Registry offers many advantages because the incidence rates used to calculate expected multiple primary cancers are obtained from the same population yielding the first primary cancers. The registry also has nearly complete reporting and a sufficiently large experience to allow comparisons to be made on an individual primary-site basis. Detailed descriptions concerning the operation of the registry have been reported (GREENBERG, 1959a; CONNELLY et al., 1968).

GREENBERG analyzed the multiple primary experience of the Connecticut Tumor Registry from 1935 through 1954. To minimize the possibility of mistaking metastatic disease for a new independent malignancy, his criteria were quite restrictive: 1) the cancer must have been specified as a second primary cancer by the reporting hospital; 2) the cancer must have been in a different anatomic site group from that in which the first primary cancer was located; and 3) an interval of 5 years must have elapsed between the diagnosis of the first primary cancer and the subsequent diagnosis of the second primary cancer. The data were analyzed in broad site groupings by using a person-years approach. He found an increased risk of cancers of the digestive system and genital organs in female breast cancer patients, and an excess of second primary cancers of the digestive system in patients with gynecologic malignancies (GREENBERG, 1959b).

BAILAR also used Connecticut Tumor Registry data to study the incidence of non-uterine tumors among uterine cancer patients. His statistical methods were similar to GREENBERG's. He restricted his definition of second primary cancers to those: 1) occurring outside the uterus, and 2) confirmed as "new and independent neoplasms" by microscopic confirmation (BAILAR, 1963).

Using GREENBERG's criteria, the findings of his previous study were reconfirmed, updated, and better defined by site within the digestive and genital systems by SCHOENBERG et al. (1969). For the first time the analysis was carried out using a digital computer. The Connecticut Tumor Registry was also used as a data resource for other investigations of the multiple primary cancer experience of patients with index tumors of the colon and rectum (SCHOENBERG and CHRISTINE, 1974), nervous system (SCHOENBERG et al., 1975), and female genital organs (SCHOENBERG and CHRISTINE, submitted for publication).

In each of these studies the excess risk of subsequent primary cancers was characterized by site, sex, and time interval following the first primary cancer. In these last three investigations, the only criterion for later primary cancer was that it be reported as such by the physician or hospital supplying the information. In all reports using Connecticut Tumor Registry material, skin cancers (other than malignant melanoma) are excluded from the tabulations. Skin cancers are often treated on an outpatient basis and consequently the tumor may not be reported to the registry.

A summary of the major papers concerning multiple primary cancers is given in Table 1. Although individual case reports and case series appear in the early portion of the table, they have generally been excluded in the review of more recent publications based on case-control comparisons. The table shows the frequency or number of multiple primary malignant tumors found by each author, together with his conclusions as to whether this occurrence is more or less frequent than expected, or whether it represents a chance phenomenon. These studies should be compared with caution. One must consider not only how many individuals were included, but also how long these individuals survived, i.e., how long they were exposed to the risk of getting a later primary cancer. The frequencies of subsequent primary cancer quoted from the various papers are not standardized for the survival of each population examined. Many of the reports listed in the table involved autopsy series in which nonsymptomatic cancers were more likely to be discovered than in clinical series. Some of these studies dealt with cancer of a particular organ or tissue, some involved both synchronous (with the multiple primary cancers appearing or being diagnosed simultaneously) and metachronous (with the multiple primary cancers appearing or being diagnosed at different times) tumors, and others restricted themselves to one type or the other. Finally, the various authors used different criteria in defining multiple primary cancer and different statistical methods in analyzing their results.

Table 1. Summary of the literature dealing with multiple primary cancers

Author	Year of publication	Total cancer patients	Cases of multiple malignant tumors		Conclusions*	Comments
			No.	% of cancer cases		
WELLS	1901	--	3	--	2	Report of one case occurring in a dog and two cases quoted from literature
WOOLLEY	1903	--	37[A]	--	1	Included skin cancers. A: Benign tumors also reported in this paper are not included in this figure
MAJOR	1918	--	628	--	1 or 2 (?)	Included skin cancer, with cases from literature and one case reported by author
KILGORE	1921	1,100	37	3.4	1	Breast was only site considered
FRIED	1928	--	--	0.1 (Estimate)	3	Report of two cases with an estimate of frequency of occurrence of multiple primary cancer
ORR	1930	1,046	8	0.8	2	Autopsy series
HANLON	1931	710	18	2.5	2	Autopsy series
WARREN and GATES	1932	1,078	40	3.7	1	Autopsy series. Figures quoted are from authors' own series. They also report statistics from other series
HURT and BRODERS	1933	2,124	71	3.3	0	Confirmation by microscopic diagnosis. Series included skin cancers
LUND	1933	1,548	94	6.0	1	Cancer of buccal mucosa
BUGHER	1934	983	30	3.1	1 or 2[B]	Autopsy series. B: Depending on type of analysis
SCHREINER and WEHR	1934	11,212	307	2.7	0	Included skin cancer
BURKE	1936	583	46	7.8	1	Autopsy series. Excluded lymphomas and leukemias
AUSTIN	1938	887	24	2.7	1	Autopsy series

Table 1. (continued)

KIRSHBAUM and SHIVELY	1938	1,411	25	1.2	1 (?)	Autopsy series
STALKER, PHILLIPS, and PEMBERTON	1939	2,500	113	4.5	1	Mostly skin cancer
WARREN and GATES	1940	1,149	237	20.6	1	First primary cancers involved skin
PELLER	1941	5,876	270	4.6	3[C]	Skin cancers were included. Of the base population, 2,146 were observed until death and 905 had an autopsy. C: See text for discussion of calculation on which conclusion was based
COOPER	1942	1,790	106	5.9	0	Skin cancer cases
PHILLIPS	1942	1,400	226	16.0	0	Confirmed by microscopic diagnosis. This series involved cancer of skin
TULLIS	1942	1,044	21	2.0	1	Confirmed by microscopic diagnosis. Autopsy series. Excluded lymphoma, leukemia, and tumors of multicentric origin
HELLENDALL	1943	685	30	4.3	1	Autopsy series
LOMBARD and WARREN	1943	1,990	117	5.9	1	Much skin cancer included in this study
SLAUGHTER	1944	--	1,868	--	1	Review of literature with addition of 40 new cases. No figures as to base cancer population are available. Cancer of the skin is included in this series
WARREN and EHRENREICH	1944	2,829	194	6.8	1	This series is a continuation of 1,078 cases reported in 1932 by WARREN and GATES. Autopsy study. Used criteria of WARREN and GATES
LOMBARD, LEVIN, and WARREN	1946	2,981	309	10.3	1[D]	These figures are for people who had died by the conclusion of the study. D: This conclusion pertains to skin cancer followed by a second skin cancer and males with lip cancer followed by multiple skin cancer

Table 1. (continued)

Author	Year of publication	Total cancer patients	Cases of multiple malignant tumors: No.	Cases of multiple malignant tumors: % of cancer cases	Conclusions*	Comments
MIDER	1946	726	21	3.0	1[E]	Only colon cancer as first primary. E: Author concluded that patients with cancer in large intestine and breast have a predisposition to new cancers in these same organs
MUSTAKALLIO	1946	1,068	119	18.6	1[F]	Only considered first primary cancers of skin. F: Predisposition in general to other cancer, especially skin cancer
WATSON	1953	16,626	1,171	7.0	2	Clinical series. Mostly skin cancer
EPSTEIN	1954	3,006[G] 879[H]	180[G] 51[H]	5.9[G] 5.8[H]	2	G: First primary malignant cutaneous neoplasm followed by a malignant neoplasm not affecting skin--data from California Tumor Registry. H: Same type of cancers as noted previously--data from Highland-Alameda County Hospital
FRIED	1958	1,514	24	1.6	0	Autopsy series
MALMIO	1959	27,712	650	2.3	0	Of the cases, 18.3% did not have a pathoanatomical diagnosis. Skin cancers are included in this study
MACDONALD	1960	9,723 6,538[I]	1,010 579[I]	10.7 8.9[I]	0	Skin cancers included. Diagnoses were confirmed by a pathologist except for multiple skin cancer. I: Excluding skin cancer of areas of skin exposed to sunlight
MOERTEL, DOCKERTY, and BAGGENSTOSS	1961	37,580	1,909 1,049[J]	5.1 2.8[J]	0	J: In different tissues. Used criteria of WARREN and GATES. Authors believe that quoted incidence rate is less than actual incidence rate
BAILAR	1963	5,366	199	3.7	1[K]	Used criteria of WARREN and GATES. First cancer in this series was always in uterine