Multiple Malignant Growths*

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In recent years a number of articles have been published on the subject of multiple primary cancers. The studies of Warren and his associates (6, 7, 8) indicate that the incidence of multiple primary cancers is sufficiently high to presuppose increased individual susceptibility. On the other hand, Peller (4, 5) has suggested that a cured cancer protects against the development of other malignant neoplasms, and has even advocated the experimental induction of a skin cancer to prevent subsequent occurrence of the more fatal cancers of other organs.

Obviously this is a question of considerable importance. If the theory that a cured tumor gives "immunity" were found to be correct, the feasibility of active "immunization" against cancer by this means would have to be considered. If the hypothesis of increased susceptibility of the cancerous individual to more than one cancer proves to be correct, the genetic-constitution hypothesis would be strengthened. In fact, the lines for future investigation may be influenced considerably by the acceptance of one or the other of these theories.

In 1943 Lombard and Warren (3) reported that more individuals were found to have multiple malignant growths than would be expected by chance (7). The validity of this finding has been questioned on the grounds that (a) skin cancer was classified by itself and not combined with lip cancer as was done by Peller; and (b) an erroneous conclusion may have been drawn because of mixed classification. This paper has been prepared to clarify these points and to test further the hypothesis that the occurrence of skin cancer "immunizes" individuals against other cancers.

In this study the data used comprised Massachusetts death records, New York State morbidity records (1), and records of patients who attended the Massachusetts Cancer Clinics through 1927-37. The records of the Massachusetts Cancer Clinics furnished the number of known multiple cancers that occurred following the first clinic visit. These were divided into 34 groups according to sex and selected sites of cancer. Persons who died in the calendar year of the first visit or the year following, as well as those alive on July 1, 1944, were omitted from the computations, since it was felt that this would give a more accurate picture than would be obtained if the entire group were included. Those who died shortly after clinic admission would have had, in some cases, multiple cancers that would have been recorded as metastases rather than as new tumors. It was found that in approximately one-half of the individuals with multiple cancers other than skin the presence of a second primary cancer was not known until death (Tables I and II). Therefore the omission of the living patients furnishes a more accurate figure on the frequency of multiple primary malignant tumors.

TABLE I: MULTIPLE MALIGNANT TUMORS DISCOVERED AT DEATH

Location	Number of tumors	Number discovered at death	Rate per 100 discovered at death
Skin—Skin	190	3	1.6
Skin—Other sites	143	82	57.4
Other sites—Skin	28	0	0.0
Other sites—Other sites	67	27	40.3
Total cases	428	112	26.2

TABLE II: PERSONS WITH MULTIPLE MALIGNANT TUMORS
RATE PER 100

Location	Dead	Living and dead
Skin—Skin	3.6	4.7
Skin—Other sites	4.2	2.8
Other sites—Skin	0.5	0.9
Other sites—Other sites	2.0	1.5
Total	10.3	9.9
Persons studied	2,981	5,078

The number of multiple cancers in each of the subdivisions was compared with an expected number [1] computed by use of person-years obtained from the clinic data, attack rates from the Massachusetts death records, and the New York morbidity records (Table III).

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[1] Method of computing an expected number described later.

TABLE III: OBSERVED AND EXPECTED METACHRONOUS MALIGNANT GROWTHS FOLLOWING PRIMARY MALIGNANT GROWTHS DIAGNOSED AT THE MASSACHUSETTS CANCER CLINICS 1927-37 AMONG PATIENTS WHO DID NOT DIE IN THE CALENDAR YEAR OF THE FIRST VISIT OR THE FOLLOWING YEAR

		Dead July 1, 1944								Living and Dead July 1, 1944	
Primary cancers	Metachronous cancers	N	Persons with metachronous cancers	Observed metachronous cancers	Expected metachronous cancers	Difference between observed and expected values	Observed − Expected / √Observed + Expected	Difference between observed and expected values if expected is: 30% greater than estimated	Difference between observed and expected values if expected is: 30% less than estimated	N	Difference between observed and expected values
Male											
Skin		745	159	234	57.0	177.0	10.4	159.8	194.2	1,348	309.3
	Skin		73	133	10.5	122.5	10.2	119.3	125.7		281.2
	Lip		6	7	2.2	4.8		4.1	5.5		10.4
	Other sites		80	94	44.3	49.7	4.2	36.4	63.0		17.7
Lip		227	33	45	15.5	29.5	3.8	24.7	34.2	481	27.7
	Skin		6	15	2.9	12.1	2.9	11.2	13.0		19.3
	Lip		4	5	0.4	4.6		4.4	4.7		8.5
	Other sites		23	25	12.2	12.8	2.1	9.1	16.5		0.1
Other Sites		445	21	27	16.4	10.6	1.6	5.7	15.6	610	14.8
	Skin		8	10	2.5	7.5		6.7	8.3		22.4
	Lip		1	2	0.6	1.4		1.3	1.6		1.4
	Other sites		12	15	13.3	1.7		— 2.3	5.7		— 9.0
Female											
Skin		435	74	99	32.0	67.0	5.9	57.3	76.7	903	108.0
	Skin		34	57	4.5	52.5	6.7	51.1	53.9		120.3
	Lip		0	0	0.1	— 0.1		— 0.1	— 0.1		— 0.1
	Breast		7	7	5.6	1.4		— 0.3	3.1		— 5.0
	Uterus		5	5	3.9	1.1		— 0.1	2.3		— 2.5
	Other sites		28	30	17.9	12.1	1.8	6.7	17.5		— 4.7
Lip		13	3	3	0.9	2.1		1.8	2.4	29	1.0
	Skin		1	1	0.1	0.9		0.9	0.9		0.8
	Lip		0	0	0.0	0.0		0.0	0.0		0.0
	Breast		0	0	0.2	— 0.2		— 0.3	— 0.1		— 0.4
	Uterus		0	0	0.1	— 0.1		— 0.1	— 0.1		— 0.3
	Other sites		2	2	0.5	1.5		1.3	1.7		0.9
Breast		593	9	9	12.9	— 3.9	0.8	— 7.8	0.1	858	— 2.9
	Skin		1	1	1.3	— 0.3		— 0.7	0.1		6.1
	Lip		0	0	0.0	0.0		0.0	0.0		0.0
	Breast		1	1	1.5	— 0.5		— 1.0	0.0		1.0
	Uterus		3	3	2.3	0.7		0.0	1.4		— 0.3
	Other sites		4	4	7.8	— 3.8	1.1	— 6.1	— 1.4		— 9.7
Uterus		303	5	5	5.6	— 0.6		— 2.3	1.1	493	— 2.6
	Skin		0	0	0.5	— 0.5		— 0.7	— 0.3		1.2
	Lip		0	0	0.0	0.0		0.0	0.0		0.0
	Breast		2	2	1.4	0.6		0.2	1.0		1.6
	Uterus		0	0	0.1	— 0.1		— 0.1	— 0.1		— 0.3
	Other sites		3	3	3.6	— 0.6		— 1.7	0.5		— 5.1
Other Sites		220	5	6	7.7	— 1.7		— 3.9	0.7	356	— 0.8
	Skin		0	1	0.9	0.1		— 0.2	0.4		4.7
	Lip		0	0	0.0	0.0		0.0	0.0		0.0
	Breast		1	1	1.5	— 0.5		— 1.0	0.0		— 0.3
	Uterus		1	1	1.1	— 0.1		— 0.4	0.2		— 0.2
	Other sites		3	3	4.2	— 1.2		— 2.3	0.1		— 5.0
Totals		2,981	309	428	150.1					5,078	

Only 4 of the 34 groups studied showed a significant difference between observed and expected values. These were "skin-skin" in both sexes, "skin-other sites" and "lip-skin" among males. If the sites of the metachronous cancers were ignored, the skin cancers of both sexes and the lip cancers of males were followed by more observed metachronous cancers than would be expected. While it is believed that the computed expected values are close to the true figure, the possibility of error exists. A 30 per cent difference in the expected values would lie well beyond any such error. Neither increasing nor decreasing the expected values by 30 per cent altered the fact of significance of the differences, but decreasing the expected by 30 per cent added "lip-other sites" among males and "skin-other sites" among females to the significant groups.

Supplementary comparisons were made using records of both the living and the dead combined. While this group is known to furnish less accurate information than the dead group, it did show considerable similarity. "Skin-skin" cases of both sexes, "skin-lip," "lip-skin," "lip-lip," and "other sites-skin" of males showed significances.

In all instances where significant differences occurred, the observed values exceeded the expected. The "skin-skin" combination showed definite significance and indicated a strong predisposition to multiple malignant growths. There is also an indication that males with lip cancers have some predisposition to multiple cancers. Immunity to the formation of a second primary cancer is not produced by the presence of a skin cancer, and while in many of the sites the figures are too small to draw conclusions there is nothing to suggest that cancer at any site produces "immunity."

DISCUSSION

Choice of Data

The observed values were the total known cancers that presumably developed after clinic admission among persons who died prior to July 1, 1944, rather than the number of persons with multiple cancers. The total number of multiple cancers was used in order to permit a better computation of the expected values. If the data had been based on the individual patients, it would have been necessary to limit the use of person-years to the period between clinic admission and the appearance of the first metachronous cancer. In many cases it was impossible to determine the correct interval.

Records of persons who had died were chosen, rather than a combination of the living and dead, for two reasons. First, their life span was completed and they could not develop a multiple cancer later. The second and more important reason was the fact that in over half of the patients with multiple cancers other than skin, the development of the second cancer was not known to the clinic until after death. Patients with multiple skin cancers usually returned to the clinic, but many of those with cancers of other organs did not. It seemed reasonable to conclude than among the living group there might be many with metachronous cancers, and a study of the dead alone would be preferable if it could be proved that this selection did not furnish an erroneous measure of metrachronous cancers.

A study based on the dead only might be criticized on the grounds that autopsied cases might affect the figures, and that the presence of a second cancer might have hastened death. Apparently neither of these suppositions was of great importance in this series. A review of the cases showed that among patients with single malignant growths 7.8 per cent were autopsied, while among those with multiple malignant growths 9.2 per cent were autopsied—a difference of 1.4 ± 1.8.

The other premise, the possible hastening of death by the presence of a second cancer, was found to be negligible by means of the following computations. The average duration of life from the first clinic visit to death for persons with single cancers and those with multiple cancers was compared. These durations were $6.80 \pm .17$ years for patients who died with multiple cancers and $4.90 \pm .05$ for those who died with only one cancer. Inasmuch as many of the cancers were of the skin, and as the probability of a skin cancer hastening death might be expected to be less than that of a cancer at another site, new durations were obtained for both groups omitting the records of persons in which skin cancer was present either alone or as one among multiple cancers. The averages were $6.40 \pm .39$ for multiples, $4.36 \pm .06$ for singles. It was suggested that the two groups might not be comparable in respect to age-sex, duration of disease prior to clinic visit, and distribution in time over the years of observation. The groups did not differ statistically from each other as to time of first clinic attendance or in duration of disease prior to clinic visit. There was a difference between the groups as to the age distribution of females. Age-sex adjustments were made and the resulting durations showed $6.62 \pm .40$ for multiple and $4.42 \pm .06$ for single cancers. The multiple cancer group persists in having the longer duration. This finding was not anticipated and was the reverse of what might have been expected. It indicates that in this study hastening of death by multiple cancers did not occur.

In order to eliminate more completely the effects of early death from severe malignant neoplastic disease, durations were computed for persons who died more than 5 years after their first clinic visit. Two such were calculated: for single cancers, and for multiples in which the second cancer was not of the skin. The results were identical; 9.4 years.

Further computations were made for males with one skin cancer and for those with multiple cancers in the "skin-other sites" group. The duration for skin cancers alone was $5.81 \pm .13$ years, for "skin-other sites" $5.52 \pm .31$ years. The difference is not significant.

The opinion seems justified that any effect a second cancer may have had in hastening death in this series of cases is so slight that it may be ignored.

Computation of Expected Values

Person-years were computed from the date of the original clinic visit either to date of death or, in the case of the living, to July 1, 1944. Expected values were computed by applying to the person-years age-sex-site specific incidence rates. These were the mortality rates for the centering point of the person-years increased by the cure rates and reduced by a correction factor when necessary.

This correction factor was required because the probability of another independent cancer, assuming independence, would be less since multiple cancer could not occur in a site already destroyed. With the skin this would have little effect, because the area involved by the primary cancer would be small in relation to the total area of the skin; with the lip it might appreciably alter the probability; with the breast at least one-half of the future probability would be lost; and with such organs as the cervix, all of it. No correction factor was used for skin cancers. The expected incidence rate for lip cancer was reduced by one-quarter, breast by one-half, uterus by nine-tenths, and all other sites by one-twentieth.

For skin, lip, and other sites in males, and skin, lip, breast, cervix, and other sites in females, age-sex specific mortality rates were obtained from a 3-year average of deaths centering on the central point of the person-years. For the dead group this was 1937, for the living and dead group 1941.

The mortality rate was changed to an incidence rate by dividing it by 100 per cent minus the percentage of cures and multiplying by 100. This was done on the assumption that the incidence rate would be the death rate plus the cure rate.

Table IV: Example of Methodology in Obtaining Expected Number of Metachronous Cancers

Age	Male skin person-years	Average, male skin cancer age specific death rates, per 100,000 population (3-year average centering on 1937)	Columns 1 × 2	Expected male skin cancers $\left(\frac{\text{Column 3}}{10} \times 100\right)$
	(1)	(2)	(3)	(4)
30–34	2.00	0.21	0.000004	0.00004
35–39	5.00	0.44	0.000022	0.00022
40–44	37.00	0.68	0.000252	0.00252
45–49	88.00	1.18	0.001038	0.01038
50–54	182.00	1.85	0.003367	0.03367
55–59	313.00	3.56	0.011143	0.11143
60–64	485.50	5.99	0.029081	0.29081
65–69	736.75	11.30	0.083253	0.83253
70–74	987.25	9.80	0.096751	0.96751
75–79	900.00	25.62	0.230580	2.30580
80 and over	630.25	94.67	0.596658	5.96658
Expected number of male skin cancers				10.52149

Lip cancers were not combined with skin cancers, as it is the belief of the authors that such a grouping is not consistent with sound pathology. Skin carcinoma is made up of two chief subtypes, the basal cell group and the epidermoid. Basal cell cancers, which make up about 70 per cent of skin cancers, practically never metastasize and have a mortality rate of about 10 per cent; indeed some observers give as low as 5 per cent. Epidermoid cancers of the skin, roughly 30 per cent of the total, not infrequently metastasize and have about 35 per cent mortality.

Cancer of the lip is a disease of mucous membranes, not of the skin. It is almost always an epidermoid carcinoma and is a much more dangerous disease than cancer of the skin. Its mortality rate, in skilled hands, is 30 per cent. Metastasis to regional lymph nodes occurs in 20 per cent of all cases, and in this group only 50 per cent are well for 5 years.

The cure rates were based on composite unpublished estimates of several authorities and computations from the New York morbidity data (2). The percentages of cures were estimated to be: skin 90; lip 70; male, other sites 5; uterus 25; breast 25; female, other sites 4.

An example of the methodology of computing expected values is shown in Table IV.

SUMMARY AND CONCLUSIONS

Expected values obtained by multiplying person-years by the age-sex-site specific incidence rate and reduced when necessary by correction factors furnished values that are believed closely to approximate the true values. The fact that similar results can be obtained even when allowing for an error in expected values far greater than would appear to be possible warrants further confidence in the conclusions.

Persons with skin cancers are predisposed to other skin cancers. There is also an indication that males with lip cancers have some predisposition to multiple skin cancers. There is no evidence that immunity to the formation of a second primary cancer is elicited by the presence of a skin cancer.

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