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Multiple Primary Malignancies

A Statistical Study Based on Autopsy Data from 1943–1972

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Summary. Autopsy data from 1943 to 1972 has been analysed for the study of multiple primary malignancies (MPM). It is shown that association between different primaries takes place at random and that there are no favourable combinations. It is further concluded that tumors do not produce either immunity or enhanced susceptibility to any subsequent malignancies of the same or any other organ. The importance of such studies is pointed out.

Key words: Multiple primary malignancy – Age distribution – Association frequencies – Cancer immunity – Cancer susceptibility.

Introduction

Th. Billroth (1889) was the first to stimulate the study of multiple malignancies, pointing out that it is possible for an individual to have two independent neoplasms developing simultaneously. Since then numerous reports have appeared on this subject. Up to a maximum of six primaries existing simultaneouslyy have been found (Ettinger et al., 1949).

The study of multiple primary malignancies (MPM) is of clinical as well as of theoretical importance. Two or more synchronous primaries of different organs may produce a pattern of symptoms which would make the exact diagnosis difficult. Alternatively one of the primaries may have such conspicuous symptoms that the other primary might remain undected.

From the theoretical point of view the question of immunity or susceptibility to cancer is of interest. If an individual with cancer is more prone to a second simultaneous or successive cancer it would mean that such individuals would need more careful followup after they received treatment for the tumor detected. However, if one cancer produced immunity against any simultaneous or successive cancers, a study of immune mechanisms in the affected individuals is of primary importance.

The present investigation was undertaken to answer the following questions: a) Are the MPM more or less frequent than they would be expected on the basis of chance, b) Are the associations between multiples random or are some associations especially favoured and c) Which of the two hypotheses (immunity or enhanced susceptibility) is valid?

Material and Methods

This paper is based on autopsy data from the Pathology Department of the Wilhelminen hospital in Vienna. The cases are derived from the urban population during the period 1943 to 1972, and a total of 42, 589 autopsy records were scrutinised. The cases selected were those in which two or more independent malignancies (including sarcomas, though these were relatively rare) of the same or of different organs, as well as of paired organs were present. Tumors of paired organs were histologically verified as distinct. For these cases the age, sex and organ effected were noted. Criteria for the definition of a primary have been discussed by various authors (Warren et al., 1932; Werthamer et al., 1961) and need not be repeated here.

An additional discriminating factor was found necessary because of multiple malignancies of the same organ (Om, 1974) or doubles of the paired organs such as breasts, ovaries etc. with a probable common hormonal determinator (Pierce et al., 1948; Speert, 1948; Wynder et al., 1969). These cases were, therefore, excluded. Further, the synchronicity was taken for granted only if the neoplasms were first verified at the time of autopsy or if one of these was detected within a year of death. We feel it is necessary to specify the 'limiting conditions' carefully as otherwise no general comparisons are possible. This aspect has not been considered rigorously by most of the previous authors.

Procedure of Calculations

From the official mortality statistics for the city of Vienna it is evident that on the average about 20–25% of all deaths are caused each year by all types of malignancy. To determine the expected number of multiple malignancies (two, three etc.) that might have been present, we proceed as follows: From the malignancy statistics for Vienna for first detections during 1970 it may be seen that malignancy was detected in 8537 males and 11209 females or in approximately 20,000 individuals. Taking the population of Vienna to be 1.7×10^6, the rate of new malignancies detected per year is about 1000 per 100,000 or 1 in 100 of the living (average of all age groups). Considering each malignancy[1] to be an independent event eith an average probability of occurrence X, the probability of two, three etc. independent events occurring simultaneously is given by the product of individual probabilities.

Assuming the 'null hypothesis' (Cook, 1966), i.e. "when one cancer has occurred in a patient, the prevelance of a second cancer at various anatomical sites is the same as the prevelance of first cancers at various sites", the average number of double malignancies expected in the viennese population per year is about 1/100th of the observed singles, that is 20,000/100=200 and the

[1] It is known that some malignancies are much more frequent than others and that they have their own characteristic age distribution. For the correct estimation of probabilities more exact calculations are necessary

number of treble malignancies would be $200/100=2$ approximately. Data of this type is not available from the official statistics as it is not the custom to keep a record of multiple malignancies. Direct comparisons are, therefore, not possible and absolute rates of occurrence cannot be determined. A documentary record of such events is urgently needed. Of a total of 42589 autopsies about a quarter or 10,000 are to expected to be due to all types of malignancy. Taking this cancer group to be identical with the non-cancer basic population, the expected number of cases with double malignancies is about $10{,}000/100 \simeq 100$ and treble malignancies to be $100/100 \simeq 1$.

In our hospital the autopsy policy has remained unchanged and as a rule hospital deaths are autopsied. In some cases in which the relatives of the deceased are emphatically against the post mortem examination or in cases in which the diagnosis has been established previously, autopsy is not performed. This is a source of error in our present considerations as some of the multiple malignancies present in the non-autopsied cases might be missed. However, there is no other satisfactory method of approaching this problem (McGregor et al., 1958; Mausner et al., 1969) and it is considered not to be a serious handicap. Our results may be considered as good approximations.

Results

The age distribution of 102 MPM (both sexes) is given in Table 1. Not included in this table are 10 cases (7 males and 3 females) of double primaries of the large intestine, 3 cases (males) with doubles of the lungs, 2 cases (males) with doubles of the stomach and 2 cases (females) with primaries of the right and left ovaries/ovarian ducts. Additional cases with three or more primaries (of which only 4 are really independent trebles) are given in Table 2.

The frequencies of association of various primaries may be seen from Table 3. It is evident that MPM of the large intestine are relatively more frequent (Garbsch et al., 1972; Om, 1974) and that other associations take place at random. The more frequent the malignancy of a particular organ (large intestine, lungs), the more frequent its association with those of the other organs although this will be affected by factors such as age and survival period etc.) For the paired organs, no decisions can be made regarding the association frequencies as their number is too small in the present sample.

Table 1. Age distribution of multiple primary malignancies (both sexes)

Sex	Age						
	30–39	40–49	50–59	60–69	70–79	80 and over	Total
Males	1	–	5	16	24	11	57
Females	–	3	9	15	12	6	45
Total	1	3	14	31	36	17	102

Table 2. Distribution of three or more synchronous primary malignancies

Number	Age	Sex	I	II	III	IV	Remarks
1	61	F	Colon descendence	Rt. breast	Lt. ovarian duct	–	
2	77	F	Uterus	Thyroid	Gall bladder	–	
3	84	F	Stomach	Rt. breast	Thyroid	–	
4	70	F	Rt. Lung	Stomach	Rectum	Colon descendence	counted as tripple
5	76	F	Rt. Ovary	Lt. Ovary	Thyroid	–	counted as double
6	66	F	Colon-Flex. lienalis	Sigma	Lt. breast	–	counted as double
7	78	F	Anus	Rt. breast	Lt. breast	–	counted as double
8	66	M	Colon ascendence	Colon descendence	Rectum	–	counted as single

Numbers 5, 6 and 7 are included in Table 1

Table 3. Association frequencies of primaries of different organs (both sexes)

	Large intestine	Lungs	Stomach/ Esophagus	Liver/ Gall bl.	Prostate	Breast	Ovaries/ Ducts	Urinary bladder	Pancreas	Uterus	Etc.
Large intestine	10	5	7	4	1	1	2	–	–	1	7
Lungs	5	3	7	2	2	–	–	1	2	–	8
Stomach/ Esophagus	7	7	2	3	2	3	–	1	1	–	7
Liver/ Gall bl.	4	2	3	–	1	–	1	–	–	–	3
Prostate	1	2	2	1	–	–	–	1	1	–	4
Breast	1	–	3	–	–	–	1	–	–	–	2
Ovaries/ Ducts	2	–	–	1	–	1	2	–	1	2	–
Urinary bladder	–	1	1	–	1	–	1	–	–	–	–
Pancreas	–	2	1	–	1	–	1	–	–	1	–
Uterus	1	–	2	–	–	–	2	–	1	–	–
Etc.	7	8	7	3	4	2	–	–	–	–	9
Total	38	30	35	14	12	7	10	3	6	4	40

Discussion

It must be pointed out that in order to define the synchronicity of multiple primaries one has to agree to particular criteria (Wynder et al., 1969) although some authors (Berndt et al., 1968) do not think it necessary to discriminate between successive and synchronous primaries. Intervals of 6 months to 5 years have been considered to be satisfactory by different authors (Moertel et al., 1961; Moertel, 1966). For the present study a limit of one year has been assumed to define the synchronicity, however, it must be admitted that it is impossible to determine how long the first tumor existed before its detection and treatment. For the following discussions these limitations must be kept in mind.

The age distribution of MPM does not show any peculiearities. During the first half of life malignancies are rare and thus multiple tumors are infrequent. Most of the multiples occur between the ages of 50 and 80.

The observed number of MPM agrees very well with the number expected. This supports the 'null hypothesis' (Cook, 1966) and demonstrates that the existence of one cancer does not make the same organ or other organs unlikely to develop a second simultaneous or successive cancer. Further, the population with one detected cancer is identical to the non-cancer population (matched for other factors) as the rate of new malignancies expected is the same in both. An individual with a neoplasm is equally prone to another malignant tumor as an individual still free from cancer. There is no enhancement of susceptibility and no development of immunity.

In a 20-year follow-up study (Spratt et al., 1966) no evidence was found for enhanced immunity or susceptibility. Immunity against or susceptibility to a second primary malignancy has previously been discussed in conjunction with multiple primaries. Depending upon the method of collecting the data some of the authors (Peller, 1941; Campbell, 1969) suggest that immunity may develop whereas others (Warren et al., 1944) conclude that there is greater tendency to the development of multiple cancers than could be produced by chance alone. It has been stated (Moertel et al., 1961) that no malignant neoplasm results in absolute immunity against the occurrence of another primary malignant tumor. Other authors have suggested that no increase in susceptibility towards a second cancer is produced by a detected cancer (Pierce, 1948; Speert, 1948), however, common etiological factors are postulated for paired organs (Wynder et al., 1969)–an hypothesis denied by Moertel (1966). The relatively higher frequency of double or multiple tumors of the large intestine (Garbsch et al., 1972; Om, 1974) would seem to favour the hypothesis of enhanced susceptibility, however, this may be due to the presence of contact carcinogens (Om, 1974).

The fact that multiple cancers arise in the same organ (large intestine) or in different organs and that they are associated at random, clearly indicates that the existence of a malignant tumor does not make the same organ or any other organ immune against second successive or simultaneous cancer.

From the present study it may be concluded that a single neoplasm neither produces immunity nor enhanced susceptibility to further malignancy. This, incidently, has important therapeutic consequences.

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