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Malignant Tumors among Twins

A Study of Divergent Views

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SUMMARY

Agreement prevails that MZ twins have higher concordance rates for cancer than do DZ twins. The exact genetic influence on concordance remains doubtful. Neither the patient groups nor the means by which data are analyzed are comparable. The naturally higher perinatal mortality rate among twins affects statistical analysis of diseases among surviving cotwins. Classification of zygosity among all studies of twins is not entirely reliable.

A review of published reports of cancer among twins notes concordance in a variety of tumors. Genetic factors appear to operate either in the concordance of the cancer or in the site of the specific tumors. A genetic origin of tumors in MZ twins is possible. Tumors, including type, site, and age of onset, affect MZ twins more than both members of a DZ pair.

Computerized permanent twin registers should be established for study of prospective follow-up of large twin populations. Suggestions are made for implementation.

Gordon Allen (1965) has stated: " The usefulness of twins in medical research is very limited and specialized ". He suggested that twin research was not so much a tool for genetic analysis as a means for testing theories about the effect of environment. Both possibilities have attracted the attention of investigators. Oliver (1965) cautioned that twins were of little use to determine genetic factors in carcinoma. In general, agreement prevails that MZ twins have higher concordance rates for cancer than do DZ twins. The exact genetic influence on this concordance remains questionable, as reported opinions differ widely (Lynch, 1967).

Problems of Twin Methodology

Part of the problem in attempting to compare studies of cancer among twins is that neither the study groups nor the means by which the data have been analyzed are comparable. According to the World Health Organization report on twins and epidemiology (1966), at least five types of twin samples have been reported: single cases, multiple cases, unselected samples of twins in a total population, volunteer series, and consecutive series. Such samplings are often of doubtful validity. In all such samples, the naturally higher perinatal mortality rate among twins adversely influences later statistical interpretations of any disease state among surviving cotwins. Many such samples make no provisions for longitudinal follow-up (Oliver, 1965).

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More than a quarter of a century ago, Greulich (1938) and Macklin (1940) suggested the existence of an intermediate type of twin pair in addition to the commonly recognized MZ or DZ pairs. Each writer cautioned that such a situation would undoubtedly influence the accuracy of twin studies. When Allen (1965) considered half-identical twins, he was able to cite several authoritative works in substantiation of this hypothesis. He pointed out the nonexistence, or extreme rarity, of opposite-sexed monochorionic twins, but observed the possibility again that occasional sets of dichorionic twins may be derived from two sperms with different paternal chromosomal complement and maternal elements of equal chromosomal complement.

The maternal elements that might lead to such a derivation are: (1) two identical blastomeres; (2) an egg and a large first polar body, each undergoing final meiotic division after fertilization (Mysberg, 1957); (3) an egg, and a second polar body (Lehmann and Huber). Students of twins have largely ignored this valid possibility and its implication on the genetic similarity and dissimilarity of twins.

The classification of zygosity among all studies of twins is not entirely reliable. Many investigators cannot obtain accurate information retrospectively. Accurate descriptions of twin placentation by obstetricians are exceptional, not general. Hospital records often provide only the number of placentas. An accurate description of placenta and membranes would provide early and substantial evidence of the type of twinning (Benirschke, 1961a, 1961b; Potter, 1963; Strong and Carney, 1967). If accurate determinations are not made at birth, the process of zygosity determination becomes increasingly more difficult later in life, especially when migration or death separates the members of the twin pair.

DZ twins of opposite sex do not present the problem. Like-sex DZ twins may be distinguished on the basis of difference in one or more of the major and minor antigenic components of the blood (Smith and Penrose, 1955). Additional methods useful to determine zygosity include detailed questionnaires (Cederlöf et al, 1961; Nichols and Bilbro, 1966), consideration of differences rather than similarities (Allen, 1965), probability calculations, and tissue transplantation experiments (Russell and Monaco, 1964). Some of the methods are simple and practical for small groups of persons under study. Others are complex, costly, and impracticable for large study groups.

A panel of 16000 pairs of twins was assembled under the auspices of the US Academy of Science for exploration of the feasibility of the accurate determination of zygosity among a large group of adults with known probabilities of error (Jablon et al, 1967). The twins' opinions of themselves were the single most reliable indication of zygosity, having an average error of 4.3%. The error in zygosity determination was 13% in the series when based on fingerprint information and recorded observations. The best figures (error, 3.2%) obtained were combinations of the twins' opinions and recorded information.

Review

Although published reports of cancer among twins are not numerous, there are case reports of concordance in a variety of tumors among twins. Cancer of the breast is most frequent (Mumford and Linder, 1936; Heizer and Lewison, 1964); concordance has also been noted in uterus (Palmer and Mitchell, 1948); gonads (Champlin, 1930; Frasier et al, 1964; Herorld et al, 1964); eyes (Brindley and Collins, 1961);

stomach (Militzer, 1935) and rectum (Protic and Prcic, 1960). In general, these reports tend to support the theory that genetic factors operate either in the concordance of cancer or in the site of the specific tumors. The significance of concordance remains in doubt, however, because of the inability to compare study groups with one another, because the materials and methods are disparate, and because not all cases of cancer among twins are reported.

Twinem (1927) observed that carcinoma rarely occurred among twins. He believed, however, that a genetic propensity toward the inheritance of certain diseases, including cancer, may exist.

McFarland and Meade (1932) reviewed various types of cancer among twins in the available publications. They strongly supported a genetic origin of tumors in homologous twins.

Madge T. Macklin (1940) reviewed the publications of tumors among MZ and DZ twins and added 15 cases. She concluded that tumors affected MZ twins far more than both members of a DZ pair. She also observed concordance in tumor type, site, and age of onset as more frequent among MZ than DZ twins. Macklin postulated that tumor discordance in MZ twins may result from: (1) extraneous factors being predominant in tumor production; (2) faulty diagnosis of monozygosity; or (3) insufficient period of observation of both members of a twin pair. Seven years later, she (Macklin, 1947) reexamined the same material and some additional twin pairs and concluded that genetically similar twins (MZ) have identical tumors far more frequently than twins who are genetically dissimilar (DZ). She emphasized that rare types of tumors were genetically determined.

Busk et al (1948) initiated a series of communications from Denmark on the subject of cancer among twins. Their first report was from material of the Danish Cancer Registry. In a series of 185 study pairs, they concluded: (1) there was a tendency toward a higher incidence of cancer among partners of MZ cancerous twins than partners of DZ twins with cancer; (2) these deviations from expected values were not considered statistically significant; and (3) there was a tendency for tumors in MZ twins to affect corresponding organs in both partners, whereas this was not the case among DZ twins.

When a second report was issued from the same institution nine years later (Nielsen and Clemmesen, 1951), 336 study pairs had been observed, but Nielsen and Clemmesen believed that their material did not warrant conclusions regarding the tendency for tumors to occur at the same site in twins who were concordant for cancer. They actually observed a slightly greater tendency for tumors to occur at concordant sites in DZ rather than in MZ twins (1 observed case vs. 0.44 expected for MZ twins, and 2 observed cases vs. 0.52 expected for DZ twins). They postulated a feeble hereditary tendency in neoplastic diseases. Thus, one of their original conclusions, that deviations from expected values were not statistically significant, did not hold up under further examination.

At about the same time, Harvald and Hauge (1956) reported on a series of 1900 pairs of twins from the Institute of Human Genetics of the University of Copenhagen.

They studied 212 twin pairs in whom cancer had occurred; cancer concordance was not considered significantly different between the MZ and DZ pairs.

In a later communication, the same investigators reported on 345 twin pairs more than 40 years of age in whom the low rate of concordance in general was striking, notwithstanding a statistically significant difference between the MZ and same-sexed DZ groups. When the material was broken down into site groups, genetic factors may have been more prominent in cancer of the breast, colon, and rectum (Harvald and Hauge, 1958).

Continued observation at the same institution led to a report (Hauge and Harvald, 1961) on 6300 pairs of twins. At that time, there were 652 twin pairs with malignant growths, of which 141 pairs were MZ and 511 DZ. Among the DZ pairs, 270 pairs were of same sex, 241 of different sex. The DZ twin pairs were classified into these two types because of the differences between them. To consider them as a single entity might complicate the comparisons between the MZ and DZ groups. The conclusion drawn from this larger study was that the rate of concordance for malignant growths in general was higher in MZ than in DZ pairs (of same or different sex). Applied to tumor sites, however, these differences were not statistically significant. Hauge and Harvald (1961) tentatively concluded that genetic factors could be considered only of limited importance in the development of malignant growths, and suggested that if differences existed between MZ pairs and like-sexed DZ pairs for concordance of malignant growths, such differences were small and less important than nongenetic factors.

That line of thinking continued in a subsequent publication concerning 6893 twin pairs, among which were 1038 cases of cancer (Harvald and Hauge, 1963). Accordingly, statistically significant differences were not found between the concordance rates in MZ and DZ like-sexed twin pairs for all types of malignant growths when pooled together. In addition, DZ pairs of unlike sex did not differ from either of the other groups. Because the relative mortality from cancer in the general population and the study material was compatible, Harvald and Hauge (1963) suggested a diversity in the population with regard to cancer which was not determined genetically to any significant extent. This opinion also applied to the question of the genetic determination of site concordance.

Another large series was reported in the United States by Jarvik et al (1960). The initial publication of the group in 1960 covered a 12-year period of follow-up for 1603 white twin index cases. When that study population was examined for cancer rates by Jarvik and Falek (1961), they observed: (1) that cancer frequency was independent of zygosity; (2) that cancer as a cause of death in senescence was as frequent in MZ as in DZ twins; and (3) that cancer was less frequent as a cause of death in the senescent age group than is expected from general statistics (9.0% vs. 16.5%).

In a subsequent communication, Jarvik and Falek (1962) regretted the lack of statistically representative twin data on cancer for the United States. They believed that their previously reported study group of 1603 index twins was suitable for such

analysis. They used 47 senescent index twin pairs, of which 24 pairs were MZ; 15 pairs, DZ same-sexed; 7 pairs, DZ opposite-sexed; and 1 pair unclassified. A concordance rate for cancer of 25% was arrived at for MZ twins, and 6.7% for DZ same-sexed twins. (These figures are not in agreement with those of the Danish investigators Hauge and Harvald, pointing to the serious error in comparing groups directly). Jarvik and Falek (1962) concluded that, in view of the difference in concordant rates, the genetic elements in cancerogenesis were operative.

Another pair of investigators in the United States, Osborne and De George (1964), were dissatisfied with conventional studies of twins employing the concordance-discordance method. They tried to determine whether or not the cancer experience of twins differed from that of the single-born, and whether it was worth-while to pursue such investigations. Their material included 152 twins and a group of 13910 single-born patients as controls. The essential difference between them was the large percentage of twin-born males with diagnosis of benign neoplastic diseases (1.94% benign vs. 1.14% malignant neoplasia). This difference did not obtain in females. The conclusions, however, were that the total cancer experience of twins did not differ from that of the single-born. They questioned genetic conclusions regarding cancer based on studies of concordance and discordance among twins.

Von Verschuer and Kober (1940) commented on the question of an inherited disposition to cancer. They could not support this thesis except for recognizing certain familial tendencies to localization in the stomach and rectum. When the twin material in their series was examined, however, they observed a greater tendency to concordance in site and type of tumor among the MZ than among the DZ twin group. Von Verschuer (1956a,b) then reexamined the material. The study group had enlarged somewhat, but the figures remained compatible with those given previously. Von Verschuer concluded that, although the occurrence of cancer appeared equal in the MZ and DZ groups, site concordance was greater among MZ than DZ twins. On that basis, he believed that hereditary predisposition to cancer was nonspecific, and, in some instances, not at all important.

Spranger and Von Verschuer (1964) again examined the same material. The span of observation for many of the twin pairs by then was over 25 years. Those investigators concluded that, although the numbers in this group were small, certain trends were evident: (1) the general cancer concordance among MZ twins was not significantly different from among DZ twins (MZ 8/29 = 0.276; DZ 28/73 = 0.384; same-sexed DZ 20/47 = 0.425; and opposite-sexed DZ 8/26 = 0.38); (2) specific concordance (same type and site) in MZ twins was more than double that of DZ twins (0.138 vs. 0.055). Spranger and Von Verschuer were of the opinion that the genetic influence was not so much one of tumorogenesis but rather of tumor localization.

Reviews from Italy (Ansaldi, 1965; Gedda, 1966) underscore the differing opinions.

Conclusions

The numbers of twin pairs available to study will doubtless increase proportionately to the burgeoning population. The future of twin studies is fairly clear. Some authors have expressed inability to draw conclusions from their own limited material (Spranger and Von Verschuer, 1964). Even when thousands or more pairs of twins are studied, the breakdown by sites and types of tumors gives small numbers for consideration (Jarvik and Falek, 1961, 1962). The suggestion of Gedda and Milani-Comparetti (1966) to form computerized, permanent twin registers for prospective follow-up of large twin populations is attractive.

1) In those nations where most births take place in hospitals, the first step in a computerized program would be to gain cooperation of institutions in regional plans, the results of which could be fed into a central computer for analysis and follow-up.

2) Twin Registries presently in operation should be urged to computerize their information, using standard terminology in order to enable study of similar problems. Such computerized information should be published in selected journals, if at all possible.

3) Follow-up for years could be more readily accomplished, despite migration and death of one of the partners, if families and twin members themselves were educated to report at specified intervals through punch cards to the Central Computer Agency.

4) Errors in zygosity determinations could be minimized by the accurate diagnosis of the type of placenta and membranes at the time of birth.

5) Blood group determinations could be done while infants were in the hospital.

6) The establishment of national libraries of information about twins would be advantageous, because of the overwhelming problem of information retrieval.

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RIASSUNTO

Si ritiene generalmente che la concordanza per il cancro sia più elevata nei gemelli MZ che nei DZ, ma la precisa influenza genetica sulla concordanza resta ancora da accertare. Né i gruppi di pazienti, né le modalità di analisi dei dati sono raffrontabili. Il tasso di mortalità perinatale, naturalmente più alto in gemelli, influenza l'analisi statistica delle malattie nei cogemelli sopravvissuti. In generale, poi, le diagnosi di zigotismo non sono del tutto attendibili.

Una rassegna delle pubblicazioni sul cancro in gemelli indica concordanza per un certo numero di tumori. I fattori genetici sembrano operare a livello sia della concordanza in generale, che della localizzazione di tumori specifici. Nei gemelli MZ, un'origine genetica dei tumori è possibile; anche per tipo, localizzazione ed età di insorgenza, i tumori colpiscono i gemelli MZ più che ambedue i membri di una coppia DZ.

Vengono avanzate alcune proposte per l'organizzazione ed il potenziamento di registri gemellari permanenti per lo studio continuato di ampie popolazioni gemellari.

RÉSUMÉ

Il existe un accord général sur le fait que la concordance pour le cancer est plus élevée chez les jumeaux MZ que les DZ, bien que l'influence génétique sur la concordance doit encore être exactement identifiée. Une comparaison n'est pas possible, ni pour les différents groupes de patients, ni pour les différentes analyses des données. Le taux de mortalité périnatale, naturellement plus élevé chez les jumeaux, influence l'analyse statistique des maladies chez les co-jumeaux survécus. En général, ensuite, le diagnostic de zygotisme n'est pas toujours certain.

Une revue des publications sur le cancer chez les jumeaux indique concordance pour un certain nombre de tumeurs. Les facteurs génétiques semblent intervenir au niveau de la concordance en général, ainsi que de la localisation de la tumeur spécifique. Chez les jumeaux MZ, une origine génétique des tumeurs est possible; aussi pour type, localisation et âge de début, les tumeurs atteignent les jumeaux MZ plus que les deux membres d'un couple DZ.

Des propositions sont avancées pour l'organisation et le développement d'un régistre gémellaire permanent pour l'étude prolongée d'une vaste population gémellaire.

ZUSAMMENFASSUNG

Übereinstimmend wird angenommen, dass die Konkordanz für Krebs bei EZ höher sei als bei ZZ, doch wurde der genaue Erbeinfluss auf die Konkordanz noch nicht festgestellt. Man kann weder Patientengruppen noch die Untersuchungsweise der Daten miteinander vergleichen. Der Sterblichkeitssatz während der Geburt, der natürlich bei Zwillingen höher ist, wirkt sich ungünstig auf die statistische Analyse der Krankheiten bei den überlebenden Paarlingen aus. Im allgemeinen sind auch die Eiigkeitsdiagnosen nicht immer ganz zuverlässig.

Wenn man sich die Veröffentlichungen über Krebs bei Zwillingen betrachtet, so ergibt sich eine Konkordanz für bestimmte Arten Tumoren. Erbfaktoren scheinen sowohl bezüglich der Konkordanz allgemein als im Hinblick auf die Lokalisation spezifischer Tumoren mitzuspielen. Bei EZ ist ein Erbursprung der Tumoren möglich; auch in Bezug auf Art, Lokalisation und Auftrittsalter der Geschwülste werden EZ mehr betroffen als beide Paarlinge von ZZ.

Es folgen einige Vorschläge zur Organisierung und Förderung permanenter Zwillingsregister, um eine dauernde Beobachtung grösserer Zwillingspopulationen zu ermöglichen.

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