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The Incidence of Male Genital Tumors: A Cellular Model for the Age Dependence

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Most human tumors, including most male genital tumors, exhibit an exponential increase in incidence with advancing age of the host. This exponential age-incidence pattern can be explained by the accumulation of mutations in the stem cells of the tissues of tumor origin. The age-incidence pattern for testicular tumors, however, is unique with a large linear increase in incidence from age 14 to 30 and a linear decline in incidence from age 30 to 60. After age 60, the incidence of testicular tumors remains low and constant.

The probability of testicular tumorigenesis is determined by the susceptibility of male germ cells to neoplastic mutation and/or the neoplastic mutagenicity of the male germ cell environment. Since there is no evidence for an environmental mutagen which is specific for male germ cells, and since male germ cells are unusually susceptible to mutation, we interpret the variation in testicular tumor incidence with age as a reflection of the susceptibility of male germ cells to neoplastic mutation. Cells are most susceptible to mutation during genome replication and we propose a model for testicular tumorigenesis which is consistent with the available data on male germ cell proliferation and with the data on testicular tumor incidence.

INTRODUCTION

The incidence of most human tumors increases continuously with advancing age of the host [1-7]. We have found that when incidence data is normalized for differences in frequency of tumor occurrence, the vast majority of human tumors exhibit very similar age-incidence patterns [7]. Testicular tumors, however, do not conform to this general pattern [8-12]. It is the purpose of this paper to describe recent and accurate incidence data for male genital tumors in Connecticut, to compare the age-incidence pattern for testicular tumors with the age-incidence patterns for other male genital tumors, and to propose an explanation for the unique age-incidence pattern for testicular tumors. The advantage of studying incidence data collected in Connecticut is twofold: The small geographic boundaries minimize variation in exposure to environmental carcinogens such as radiation, chemical pollutants, and possible viruses, and the affluent urban population with its abundance of physicians tends to minimize the danger of under-reporting and incorrect diagnosis.

MATERIALS AND METHODS

Data for the annual incidence of malignant tumors of the male bladder, testis, prostate, penis, and other male genital loci from the beginning of 1968 through the end of 1978 was collected by the Connecticut Tumor Registry, Hartford, Connecticut. We were concerned with the variation in tumor incidence with hose age and not

with differences among the tumors in frequency of occurrence. In order to normalize age-incidence patterns for differences in frequency of occurrence, the incidence data was treated as described previously [7]. For each tumor, the annual incidence per 100,000 persons at each age was averaged between 1968 and 1979. Then, for each tumor, this average annual incidence per 100,000 persons at each age was summed over all ages to give total incidence. The percentage of this total incidence which occurred at each age was then calculated (Fig. 1).

RESULTS

The normalized age-incidence patterns for male bladder and genital tumors other than tumors of the testis are all very similar (Fig. 1). As a basis for comparison to the normalized age-incidence pattern for testicular tumors, we calculated the average normalized pattern among all male bladder and genital tumors other than tumors of the testis. In Fig. 2, this average pattern is displayed on a logarithmic incidence scale. The difference between the data in Fig. 2 and the least-squares straight line is insignificant ($p > 0.3$) according to the chi-square test. We conclude that the incidence of male bladder and genital tumors other than tumors of the testis increases exponentially with age and, on the average, can be described by the following equation:

$$\log \% \text{ total incidence} = 0.042\,(\text{age}) - 1.99$$

The normalized age-incidence pattern for tumors of the testis is unique (Fig. 1). The incidence of testicular tumors increases linearly from age 14 to some age between

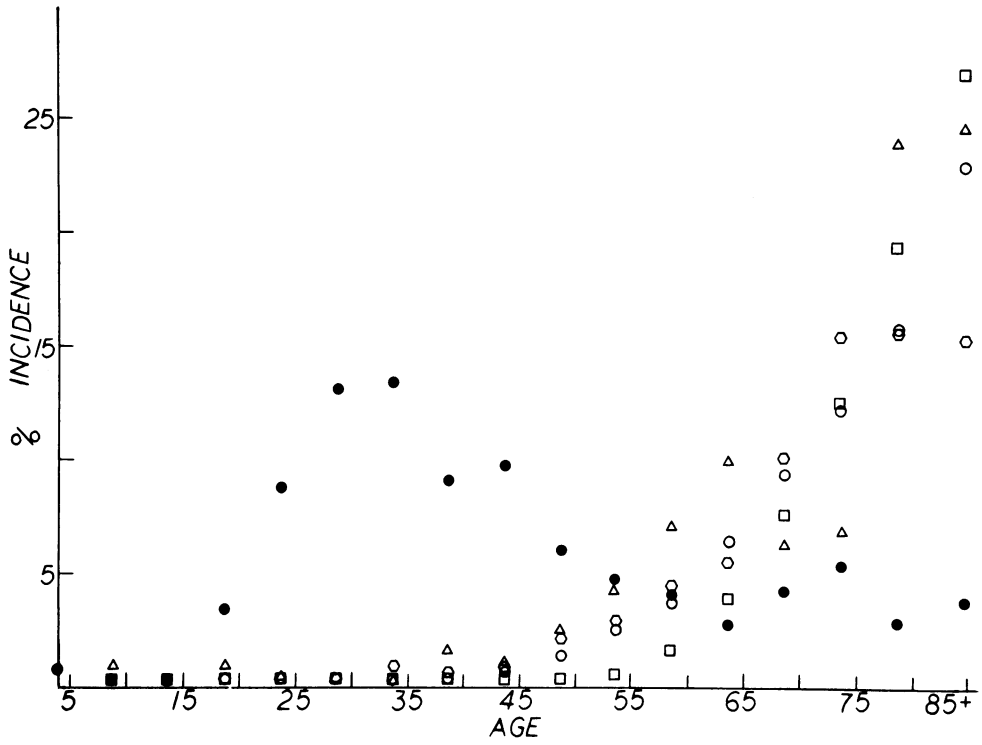

FIG. 1. Percentage of total incidence of tumors of the male bladder (○4023 cases), testis (●512 cases), penis (⊂⊃142 cases), prostate (□8102 cases), and other male genital tumors (△43 cases) which occurred per 100,000 persons at each age in Connecticut from 1968 through 1978.

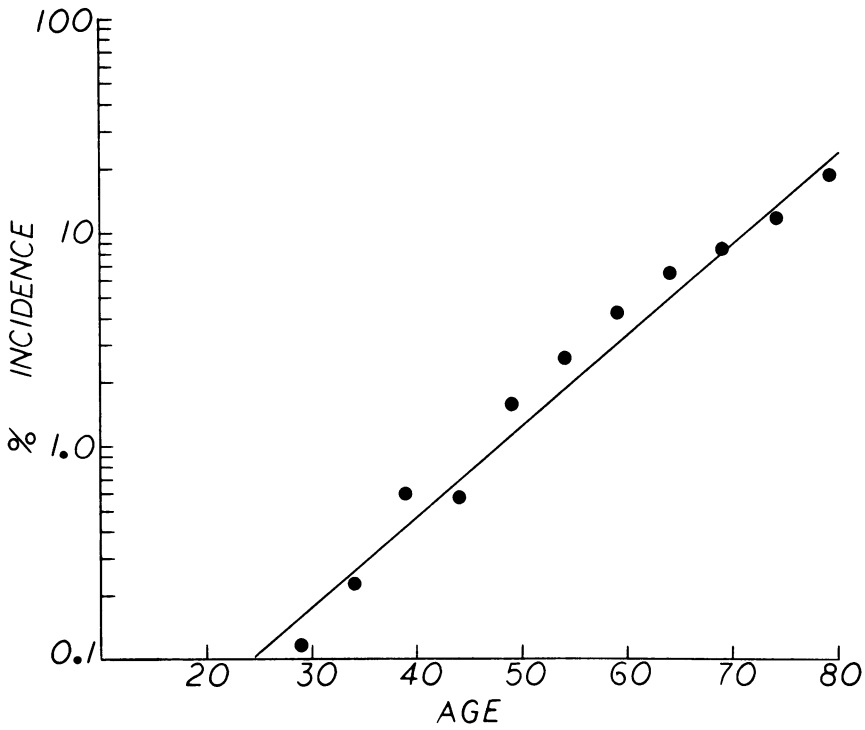

FIG. 2. Percentage of total incidence averaged for tumors of the male bladder, penis, prostate, and other male genital tumors excluding tumors of the testis which occurred per 100,000 persons at each age in Connecticut from 1968 through 1978 and the least-squares straight line.

29 and 34. Points on the least-squares straight line describing the data between ages 14 and 29, for instance, are not significantly different ($p > 0.3$) from the data points in Fig. 1, according to the chi-square test. Thus the incidence of testicular tumors between ages 14 and 29 can be described by the equation for the least-squares straight line:

$$\% \text{ total incidence} = 0.884 \text{ (age)} - 12.66$$

The incidence of testicular tumors decreases linearly from age 34 to some age between 59 and 69. Points on the least-squares straight line describing the data between ages 34 and 59, for instance, are not significantly different ($p > 0.3$) from the data points in Fig. 1, according to the chi-square test. Thus the incidence of testicular tumors between ages 34 and 59 can be described by the equation for the least-squares straight line:

$$\% \text{ total incidence} = -0.360 \text{ (age)} + 24.57$$

The incidence of testicular tumors is rather constant at ages greater than 60 and there is a very small peak in incidence (less than 1 percent of total testicular tumor incidence) at ages less than five (Fig. 1).

DISCUSSION

The normalized age-incidence patterns for male bladder and genital tumors other

than tumors of the testis (Fig. 2) resemble the normalized age-incidence patterns for the vast majority of human tumors and are consistent with the model previously proposed [7]: mutations which accumulate during normal aging cause or facilitate neoplastic mutations. Cells are most susceptible to mutation during genome replication [13] and the accumulation of mutations during aging by lifelong genome replication is consistent with current models for both epithelial [13] and hematopoietic [14-16] stem cell propagation.

Our age-incidence pattern for testicular tumors in Connecticut resembles the recent age-incidence pattern for testicular tumors in Los Angeles [8] and older age-mortality patterns for these tumors [9–10]. The advantage of our normalized age-incidence pattern for testicular tumors is that it permits comparison with recent normalized age-incidence patterns for other tumors. On the basis of such a comparison, the linear age-incidence pattern for testicular tumors is found to be unique among male genital and bladder tumors (Fig. 1) as well as among all other tumors studied [7]. The unique age-incidence pattern for testicular tumors is incompatible with the model for carcinogenesis previously proposed [7].

The vast majority ($>$ 94 percent) of testicular tumors are of germ cell origin [11]. We consider the probability of testicular tumorigenesis to be determined by the susceptibility of germ cells to neoplastic mutation and/or the neoplastic mutagenicity of the germ cell environment. Although some aspects of epidemiology have been interpreted as suggesting a role for an environmental agent in testicular tumorigenesis [20–23], there is no evidence for any specific etiologic agent in the environment [9,19]. The finding that tumors of male genital loci other than the testis display conventional exponential age-incidence patterns (Fig. 2) indicates that if environmental mutagenicity is the primary determinant of the unique age-incidence pattern for testicular tumors, the mutagen must be specific for the testis rather than the male genital area. This requirement for exquisite tissue specificity would exclude radiation and known chemical carcinogens.

We have concluded that tissue susceptibility to neoplastic mutation is the dominant determinant of the age-incidence pattern for the vast majority of human tumors [7,24] and we suggest that the unique age-incidence pattern for testicular tumors can best be interpreted as a reflection of the variation with age in germ cell susceptibility to neoplastic mutation.

Continuous genome replication as exhibited by epithelial [13] and hematopoietic [14–16] stem cells would yield an exponential increase in susceptibility to neoplastic mutation with advancing age of the host [7,24]. The linear increase and decline in testicular tumor incidence between ages 14 and 59 (Fig. 1) suggests a unique variation in male germ cell susceptibility to neoplastic mutation.

The beginning of the linear increase in incidence of germ cell tumors at age 14 (Fig. 1) coincides with the beginning of rapid germ cell proliferation at puberty [25–26]. Rapid proliferation is accompanied by rapid genome replication and increased susceptibility to mutation [13]. Male germ cells are unique in that they serve no purpose for the host unless they are emitted. Because male germ cells are designed for emission, mutation repair mechanisms can be lax without conferring a survival disadvantage upon the host. Indeed male germ cell mutations must be common since it is not abnormal to find 30 percent of the emitted spermatozoa to be atypically formed [27]. We propose a model for male germ cell proliferation (Fig. 3) to account for a linear variation with age in male germ cell susceptibility to neoplastic mutation.

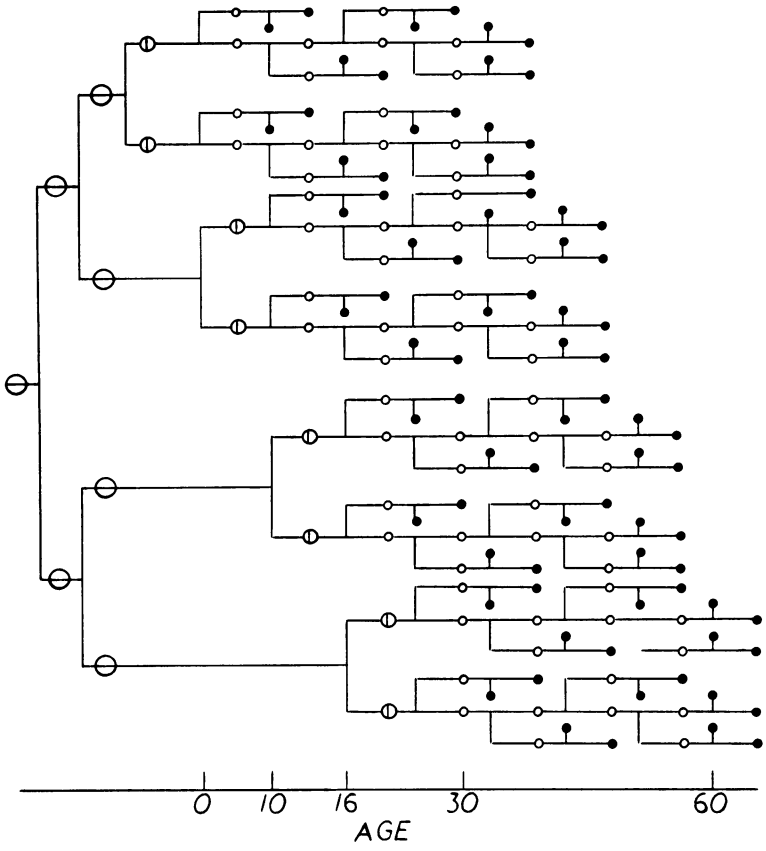

FIG. 3. Model for testicular germ cell proliferation: ⊖, primordial germ cell and/or prospermatogonium; ⊕, primitive spermatogonium, i.e., Clermont's dark type A [28–29]; ○, proliferating spermatogonium, i.e., Clermont's pale type A [28–29]; ●, committed spermatogonium, i.e., Clermont's type B [28–29]. Primordial germ cells and prospermatogonia proliferate before birth [25]. At birth some spermatogonia are present [25] but the number of spermatogonia per testis remains rather constant until age 10 [25–26]. Between ages 10 and 16, the number of spermatogonia per testis increases exponentially [26]. We attribute the linear increase in tumor incidence between ages 14 and 30 to a linear rate of activation of clones of primordial germ cells or prospermatogonia. Most testicular tumors occurring between ages 14 and 30 resemble primordial germ cells histologically [11,30–31]. Once activated, clones of spermatogonia would proliferate according to the mechanism described by Clermont [28–29]. Stem cells have a finite life span [32] and we attribute the linear decline in tumor incidence between ages 30 and 59 to a linear rate of inactivation of the clones of proliferating spermatogonia. Similar rates of activation and inactivation of clones of spermatogonia would explain the similarity between the rates of increase and decline in tumor incidence. Because committed spermatogonia are destined to become spermatozoa [28–29], they have a minimal capacity for division and thus a minimal opportunity to acquire neoplastic mutations [13]. This pattern of germ cell proliferation is consistent with testicular tumor histology which resembles spermatogonia after age 30 [11,30–31] and committed spermatogonia after age 60 [11,30–31]. The absence of proliferating spermatogonia after age 60 is consistent with the diminished fertility of elderly men [33] and can explain the low and constant rate of testicular tumor incidence after age 60.

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