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Carcinogenesis: A Cellular Model for Age-dependence

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Abstract. *Background: Certain characteristics of cancer remain invariant between populations, the age of peak risk, the age ranges of significant and insignificant risk, and the pattern of risk variation with age. We offer an explanation that is built by analogy on that for trisomy 21. Materials and Methods: We calculated the rate of change in risk with age for the most common cancers, death from all causes, trisomy 21/birth, and trisomy 21/1000 women. Results: Beyond some milestone age, the risk of death from all causes and trisomy 21/birth exhibit constant acceleration, while risk of cancer and trisomy 21/1000 women exhibit increasing deceleration. Conclusion: With advancing age, the risk of abnormal cell division increases continuously but remains harmless until some tissue-specific milestone, e.g., depletion of stem cells, and is then damped by a continuous decline in rate of cell division.*

Because the risk of contracting the common cancers increases dramatically with advancing age, it is tempting to conclude that the aging process is carcinogenic, *e.g.*, "advancing age is the most potent of all carcinogens" (1-2). To avoid being deceived, however, we must distinguish two different aspects of aging. On the one hand are the milestone events that appear at characteristic ages, *e.g.*, growth, puberty, menopause, and senility, while, on the other, are those cumulative processes that span a lifetime, *e.g.*, loss of organ reserve (3), telomere shortening, memories, and risk of dying. Clearly, those cancers that exhibit peak risk in childhood, *e.g.*, acute lymphoblastic leukemia, cerebellar and brain stem tumors, neuroblastoma, retinoblastoma, Wilm's tumor, osteogenic and Ewing's sarcomas, and rhabdomyosarcomas (4), or in middle age, *e.g.*, testicular cancer and Hodgkin's disease (5-6), cannot be caused by any cumulative effect of aging. What is equally clear, but less well known, is that the common cancers exhibit peak risk in the latter years of life, and, therefore, cannot be caused by any cumulative effect of aging (7-10).

The plot of cancer incidence rate *vs* age consists of three parameters which can vary with tumor type, position on the incidence axis, position on the age axis, and shape. Position on the incidence axis is sensitive to time and place, and manifests variations in genetic susceptibility and environmental carcinogenicity (7-10). For cancers of the testis, ovary, endometrium, female breast, lung, colon, rectum, stomach, and prostate, however, position on the age axis and the shape of the age-incidence pattern are independent of position on the incidence axis (7-10). These, and probably most tissues of tumor origin, exhibit four carcinogenic characteristics that remain invariant from one population to another: i) age range of insignificant risk, ii) age range of significant risk, iii) age of peak risk, and iv) pattern of variation in risk with age (7-10). We attribute these fixed aspects to aging genes that remain constant among all people (10). The same four characteristics apply to the risk of cell division anomalies such as trisomy 21 (11) and we imagine that this risk is due to similar aging genes.

A theory of carcinogenesis must explain: a) the transition from age range of insignificant to age range of significant risk, b) the decline in risk after age of peak risk, and c) the pattern of variation in risk with age. It is the purpose of this paper to offer such a theory. It is built by analogy on the explanation for the age-dependent risk of trisomy 21, the most common chromosomal abnormality (11-12).

Materials and Methods

Age-specific cancer incidence rates (cases/100,000 people of specified age/year) for the most common cancers in each gender in Connecticut in 2001 were obtained from the Connecticut Tumor Registry, USA (13). The number of diagnoses from which these rates were calculated are as follows: for female cancers, breast = 2935, lung = 1113, colon = 823, and uterine corpus = 553, and for male cancers, prostate = 2895, lung = 1322, colon = 714, and bladder = 673. For each cancer, we plotted the age-specific incidence rates *vs* age and connected the data by a smooth curve. The data for ages designated 85+ were plotted at age 90. We used this smooth data to determine the change in cancer incidence rate

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Table I. *Age-dependent change in rate of cancer incidence and death from all causes in males.*

Ratio of ages	Ratio of rates				
	Cancer incidence				Death all causes
	Prostate	Lung	Colon	Bladder	
45/40	2.14	4.00	2.00	1.40	1.43
50/45	4.00	2.00	2.10	1.43	1.50
55/50	3.33	2.25	1.90	3.00	1.52
60/55	2.20	1.78	1.70	2.13	1.53
65/60	1.64	1.63	1.63	1.76	1.50
70/65	1.47	1.50	1.45	1.55	1.53
75/70	1.04	1.35	1.43	1.37	1.59
80/75	0.87	1.05	1.30	1.33	1.53
85/80	0.71	0.95	1.20	1.09	1.53
90/85	0.65	0.81	1.06	1.04	1.40

Table II. *Age-dependent change in rate of cancer incidence and death from all causes in females.*

Ratio of ages	Ratio of rates				
	Cancer incidence				Death all causes
	Breast	Lung	Colon	Uterine Corpus	
45/40	1.49	2.40	4.50	5.0	1.73
50/45	1.41	2.25	2.22	2.13	1.63
55/50	1.27	2.26	1.65	1.56	1.61
60/55	1.21	1.80	1.82	1.66	1.60
65/60	1.17	1.55	1.50	1.27	1.63
70/65	1.17	1.54	1.50	1.06	1.51
75/70	1.08	1.23	1.41	1.03	1.58
80/75	0.98	1.10	1.34	1.01	1.77
85/80	0.92	0.76	1.24	0.92	1.60
90/85	0.94	0.71	1.03	0.57	1.64

with age. For each cancer, we calculated the ratios of rates for adjacent age categories, *i.e.*, the ratio of cancer incidence rate at age 45 to that at age 40, at age 50 to that at age 45, at age 55 to that at age 50, *etc.*

Age-specific rates of death from all causes in the U.S. in 2001 were obtained from the National Center for Health Statistics (14). For each gender, we plotted the death rates *vs* age and connected the data by a smooth curve. Rates for ages designated 85+ were plotted at age 90. We used this smooth data to determine the change in death rate with age as above.

Age-specific fertility rates (births/1000 women of specified age) in 2000 in the U.S. were obtained from the U.S. Census Bureau (15). These rates, 69.7, 91.8, 107.9, 87.0, 45.1 and 10.9 were plotted *vs* the midpoints of their respective age ranges, 15-19, 20-24, 25-29, 30-34, 35-39 and 40-44. The data were connected by a smooth curve and used to determine rates at individual ages by interpolation. Age-specific risks (% of births) of trisomy 21 were obtained from the Atlas of Genetics and Cytology in Oncology and Haematology web site (11). These risks, <0.1%, 0.2%, 0.5%, 0.7%, 1.0%, 2.5%, 5% and 15% were plotted *vs* their respective ages, <30, 34, 38, 39, 41, 44, 46 and 50. The data were connected by a smooth curve and used to determine risk at other ages.

Results

Statistics. Tables I and II show the rate of change in cancer incidence rate with age for the most common cancers in each gender in Connecticut for 2001. Notice that for each cancer, there is a gradual and continuous decline in rate of increase, *i.e.*, a deceleration of risk. The Tables also show the rate of change in rate of death from all causes. Notice that the rate of increase in mortality with age stays constant throughout life and differs dramatically from the deceleration of cancer risk.

Table III shows the rate of change in age-dependent risk/birth and incidence rate of trisomy 21. The risk/birth increases exponentially from before age 30 to menopause (11-12) and the ratio of risk at adjacent ages resembles the pattern for mortality rates, but not cancer incidence rates. Fertility rates decline with age and the incidence rate of trisomy 21 peaks and then declines with advancing age in the manner typical of cancer.

Model. The variation in age-specific mortality rates with age is a convenient proxy for the aging process (3, 16). With advancing age, the genome becomes less stable (2) and cell division anomalies more common, as is evident in the risk of trisomy 21. Because this risk accelerates with age in a manner resembling the risk of death from all causes, we suspect that aging is due to genetic or epigenetic changes that cause cell division anomalies. Because the age-specific

Table III. *Age-dependent risk and incidence rate of trisomy 21 in 2001.*

Age	Risk/Birth (%)	Fertility rate (Births/1000 women)	Incidence rate (Cases/1000 women)
32	0.10	88	0.088
33	0.15	82	0.123
34	0.20	72	0.144
35	0.30	64	0.192
36	0.40	56	0.224
37	0.45	46	0.207
38	0.50	36	0.180
39	0.70	26	0.182
40	0.85	21	0.179
41	1.0	16	0.160
42	1.2	11	0.132

risk of cancer decelerates with age, we conclude that these genetic or epigenetic changes are not sufficient to explain carcinogenesis. Because the age-specific risk/woman of trisomy 21 decelerates with age in a manner resembling the risk of cancer, we suggest that some analogous modulation of the genetic or epigenetic causes of cell division anomalies is involved in carcinogenesis. In the case of trisomy 21, the modulation consists of factors that inhibit fertilization. In the case of carcinogenesis, it is likely to be factors that inhibit cell division. We offer the following model: In the age range of insignificant risk, stem cells in the tissues of tumor origin can acquire genetic and epigenetic changes but are prevented from forming tumors by a commitment to terminal differentiation. Thus, the changes remain dormant until some critical age which is peculiar for each tissue of tumor origin. At this critical age, the tissue-specific stem cells are depleted and cell replacement must occur by a different mechanism, *e.g.*, dedifferentiation. These cells are then able to form tumors and the risk of cancer increases with age as more are recruited into cell division. However, the rate of cell division declines with age and, thus, the risk is gradually and continuously decreasing until, eventually, risk plateaus and declines with advancing age.

Primary oocytes are terminally differentiated germ cells. Only a minute fraction (one/month through the menstrual years) enter a proliferative phase. In this phase, the germ cells express the consequence of aging as risk of trisomy 21. Somatic cells would express the same consequence as risk of cancer. Before puberty and after menopause, the risk of trisomy is zero. We suggest that similar age-dependent blocks on cell division in the tissues of tumor origin prevent cancer at early and late ages. It is interesting that the age of onset of significant risk for the common cancers, 30-40 years, corresponds to the average life expectancy throughout evolutionary history (3, 17). Thus, there was no reason to program tissue-specific stem cells to divide beyond this age. Cancer may be the consequence of outliving this original strategy for terminal differentiation. As life expectancy increased, a new strategy was needed for cell replacement. One such strategy is dedifferentiation (18-20). However, as cells dedifferentiate, their accumulated genetic and epigenetic damage make them available for carcinogenesis. However, the rate of cell division declines with age (21-22) and, thus, the risk of cancer follows a continuously decreasing rate. Eventually risk pleateaus and declines with increasing age.

Discussion

Cancer age-incidence patterns in populations distributed across the globe show enormous variation in position on the incidence axis at any given age, but remarkable constancy in age at half total incidence and in shape (7-10). In addition, these studies show the impact of age variation on incidence rate to be much greater than the impact of genetic or environmental variation. From these studies, we concluded that the role of aging in carcinogenesis is dominant to that of the environment and that it is determined by aging genes that are the same in all people. But all cancers studied show a gradual and continuous deceleration in risk with age through the latter years of life (7-10). Thus, the role of aging in carcinogenesis is of a milestone nature and not cumulative. The data on atomic bomb survivors demands this conclusion.

Ionizing radiation is a non-specific carcinogen that increases the risk of a wide variety of cancers. In atomic bomb survivors (23), these risks did not appear until the age at which the respective cancers appeared in the unexposed population: "The increase in site-specific cancer mortality occurs only at the age at which the natural incidence increases. There is still no evidence that radiation-induced cancers appear earlier than other cancers of the same sites" (24).

Like radiation, obesity and tobacco smoke increase the risk of a variety of cancers, but there is no evidence that obesity or smoke-induced cancers appear earlier than the same cancers in normal-weight subjects and non-smokers (25-26). Carcinogenetic damage can be acquired at early ages, *e.g.*, "radiation-related cancer risks generally decrease markedly with increasing age at exposure" (27), but are not

expressed until passage of some age milestone. BRACA genes, for instance, increase the risk of breast and ovarian cancer enormously (28). They are present from birth and cause cell division anomalies (29), but do not cause cancer to appear earlier than in non-BRACA patients (28). Similarly, diethylstilbestrol exposure *in utero* increases the risk of vaginal and testicular cancer, but not before adolescence (30). It is as if some protective block were lifted at the tissue-specific age milestone; once this block is lifted, risk increases at a rate that is influenced by events prior to the milestone.

Some hereditary conditions, such as in familial adenomatous polyposis and hereditary non-polyposis colon cancer, do hasten the appearance of cancer. We suspect these conditions act as tissue-specific premature aging syndromes causing premature depletion of committed stem cells.

Inflammation in childhood predisposes to cancer in the elderly (31), perhaps by creating the epigenetic changes that foster cell division anamolies (32-33). Indeed the mortality rate in infancy predicts the mortality rate from childhood through the elder years (31). Until recently, the mortality rate was determined by avoidable causes (3, 31). As these causes diminished over time, the mortality rate declined, but the rate of change in mortality rate with age has remained fixed (31), and the milestones, therefore, are unchanged.

Caloric restriction (CR) delays carcinogenesis while also inhibiting growth, inflammation, and oxidative damage, and increasing life-span by complicated interactions between SIRT1, Foxo3a, and p53 (34-35). Some of these interactions show divergence between the aging process and carcinogenesis. Apoptosis and senescence, for example, protect against cancer but diminish longevity (35-37). Further, some defects in DNA repair cause cancer without accelerating the aging process, while others do the reverse (38). Clearly, not all aspects of the aging process are carcinogenic. We suggest that some tissue-specific milestone is, and that CR postpones it. What is this milestone? We suggest it is the depletion of tissue-specific stem cells. After this milestone, cell replacement becomes dependent on a different mechanism, *e.g.*, dedifferentiation, and this mechanism is susceptible to carcinogenesis.

Premature aging syndromes are known to accelerate the appearance of cancer and we suggest that these syndromes operate in a manner opposite CR, *i.e.*, by hastening the depletion of tissue-specific stem cells. Werner Syndrome, the most common premature aging disorder, is inherited, but not expressed before adolescence. Werner cells are defective in DNA replication (39), but what accounts for the decades-long lag before cancer appears? We suggest the lag is required to deplete tissues of the stem cells that are committed to terminal differentiation. Until this population is depleted, even defective DNA replication cannot cause cancer. Once it is depleted, cell replacement comes at the loss of a differentiated cell and the gain of cancer potential. If our reasoning is correct, factors that prolong stem cell survival (40-41) should protect against cancer and delay the onset of aging.

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