Letter to the Editor

Does Prostate Cancer Start at Puberty?

Prostate cancer is the most common cancer among males in North America (1). To date, there are very few clues as to the etiology and pathogenesis of this cancer. Recently, two reports have implicated dietary fat and components of fat as prostate cancer risk factors (2,3). Ross and Henderson (4) have proposed a model for prostate cancer pathogenesis that unifies prostate cancer risk factors including "gonadostat" set points in utero, prolonged exposure to testosterone levels in childhood and adulthood, increased consumption of fat, and low consumption of fiber. All these risk factors presumably act to increase expression of 5α-reductase, which leads to increased intracellular dihydrotestosterone levels and increased prostate cell division.

Prostate cancer incidence becomes significant at around age 40 and continues to increase throughout the lifespan. The mean age of patients diagnosed with prostate cancer is ~64 years (5). At diagnosis, the mean volume of the prostate cancer is ~5cm^3 (5), which is equivalent to ~5×10^9 cancer cells (6). Recently, we estimated prostate cancer cell doubling times in vivo by serially monitoring prostate specific antigen levels in the serum of prostate cancer patients after radical prostatectomy (7). We found that serum PSA levels change according to the equation

$$[PSA]_t = [PSA]_o e^{Kt}$$

where $[PSA]_t$ is the PSA concentration at any time t, $[PSA]_o$ is the baseline PSA concentration postsurgery, and K is a constant. The value of K can be calculated experimentally as the slope of the plot of ln [PSA] versus time. The doubling time is then equal to td = ln2/K. We have experimentally verified that the plot of ln[PSA] versus time is linear (7).

We have calculated doubling times for 10 patients who ultimately relapsed and found the values to be between 67 and 568 days. The mean doubling time was 277 days and the median 265 days.

Assuming that the mean tumor volume at diagnosis is equivalent to 5×10^9 tumor cells, we could calculate the time required for one tumor cell to proliferate until the tumor is diagnosed. The results at three different doubling times, i.e., 67, 265, and 568 days, are as follows: 5.9, 23.5, and 50.2 years, respectively. These numbers were calculated by assuming that tumor cells proliferate exponentially, i.e., $C = Co.e^{Kt}$ where Co = 1 cell and $C = 5\times10^9$ cells at diagnosis. Hence, t = lnC/K.

These data suggest that, in at least some prostate tumors, the initiating event occurred at an age of ~14 years. Based on this information, we speculate that very early during life, and especially around puberty, when there is an abrupt and massive increase of androgenic steroid hormone production by the testes, one or few prostate cells undergo malignant transformation and start to proliferate with doubling times ~600 days. These cells will eventually give rise to tumors diagnosed at ages ~60–70 years. We speculate that any time during the course of this process, additional genetic alterations may occur in the tumor cells, which will give rise to tumor cells with shorter doubling times. Apparently, such events may occur at any age. Our data suggest that the mean age of such events might be 40.5 years (64 years minus 23.5 years), but it could be as long as 58.1 years (64 years minus 5.9 years).

The speculation of an initiating event in prostate cancer around puberty and the change of the cancer cell phenotype due to additional genetic alterations is in agreement with theories supporting multiple genetic alterations in other cancers (8).

These data suggest that at least some forms of prostate cancer initiate at puberty and follow a slow but steady course until they are diagnosed at ages 60–70 years. Our speculation that other prostate cancers also occur during puberty, but the tumor cells shorten their doubling times because of additional genetic alterations needs further investigation. Our hypothesis for cancer initiation during puberty also may be applicable to other endocrine cancers such as breast cancer.

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