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Letters to the Editor

Correspondence re: E. Farber, Cell Proliferation as a Major Risk Factor for Cancer: A Concept of Doubtful Validity. Cancer Res., *55:* 3759–3762, 1995.

Letter

The September 1, 1995 issue of *Cancer Research* features a "Perspectives in Cancer Research" article on cell proliferation as a risk factor for cancer (1). Emmanuel Farber offers the provocative concept that cell turnover and replication have little or no impact upon the risk of cancer induction. His proposal, however, includes conceptual errors that must be corrected:

1) "It is now well documented that atrophic gastritis, with low levels of cell proliferation, not hyperplastic or hypertrophied gastritis, is a risk factor for the development of cancer."

On the contrary, the rate of cell turnover with autoimmune atrophic gastritis is actually increased in response to accelerated cell loss in the glandular epithelium (2). Intestinal metaplasia of the atrophic stomach is also associated with increased risk of cancer, as is Barrett's metaplasia of the distal esophagus, and each of these is characterized by increased rates of cell replication (3, 4). A similar phenomenon is observed with ulcerative colitis (5) and celiac disease (6). These two conditions, like autoimmune gastritis, are associated with an increased risk of cancer induction.

2) "It is now well documented that many, if not all, genotoxic carcinogens are inhibitors of DNA synthesis and/or cell proliferation."

The described phenomenon is an effect of the induction process rather than a risk factor for induction.

3) "Pregnancy is associated with a vigorous cell proliferation of all epithelial cells of the breast, yet is associated with decreased risk for breast cancer."

Women are especially vulnerable to the effects of X-ray-induced genotoxic damage during their adolescent years, when glandular proliferation is at its peak. This accounts for the increased risk of breast cancer among women who have received X-ray therapy for Hodgkin's disease during adolescence (7) and the limitation of increased breast cancer risk among Hiroshima women exposed to the atomic bomb to those who were adolescents or young adults at the time of exposure (8).

Increased vulnerability to cancer induction need not result in cancer if the vulnerable cells are not challenged by a genotoxic event. This probably accounts for the infrequent cancers in the human jejunum and ileum. The bacterial counts of the small bowel are much lower than those of the colorectum, and anaerobes are usually absent (9). *Clostridia*, *Bacteroides* sp., and coliform organisms are usually absent in the proximal small bowel or are present in only very small numbers. It has been argued that carcinogens in the colon are generated from bile salts as metabolites of anaerobic bacteria (10), and cancer vulnerability is not tested in their absence. This also accounts for the late onset of some cancers in families affected by hereditary nonpolyposis colon cancer. This dominant mutation in mismatch repair genes has low penetrance (11). The defect does not surface in the absence of genotoxicity.

Although the risk of cancer induction of some cancers may be unrelated to the rate of cell proliferation, it would seem premature to discard cell turnover as a risk factor in all primary sites. It would seem to have an especially strong influence upon the risk of cancer of the gastrointestinal tract.

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Letter

The article in *Cancer Research* by Emmanuel Farber (1), which attacks the idea that cell division is important in cancer causation, did not deal with the literature adequately or critically. Mutagenesis, and thus carcinogenesis, is increased by increasing either DNA damage or cell division in cells that are not discarded. There is, in fact, quite persuasive evidence that cell division is an important factor in mutagenesis and carcinogenesis.

1) There is enormous endogenous DNA damage from normal oxidation, and the evidence suggests that oxidative damage is a major factor not only in aging but in the degenerative diseases of aging such as cancer (2). The steady-state level of oxidative damage in DNA is over one million oxidative lesions per rat cell (2). Thus, because there is endogenous DNA damage, the cell division rate must be a factor in converting lesions to mutations and thus cancer (3). Raising the level of either DNA lesions or cell division will increase the probability of cancer. Just as DNA repair protects against lesions, p53 guards the cell cycle and protects against cell division if the lesion level gets too high; however, neither defense is perfect (4). Cell division is also a major factor in loss of heterozygosity through nondisjunction and other mechanisms (3).

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