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Cag Repeats and Cancer Probabilities – Not A Hard and Fast Rule

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Abstract

The most important hallmark of cancer is the inadvertant mutations in both nuclear and mitochondrial genomes. The etiology for such mutations is multi-factorial and the predominant one among them is the chemical mutagens / carcinogens. The association between environmental contaminations either by carcinogenic chemicals or by the soil radiations have been well established in some geographical conditions or situations where a small population of individuals has been subjected to such chemicals or radiations. In such geographical areas the carcinogen or radiation sensitive cells in the human may be undergoing mutations in a cumulative fashion. In such geographical areas, the rate of incidence / prevalence of cancers have been witnessed in high percentage than the normal counterpart locales (Indra and Ramalingam 2013).

Besides the above environmental causes, the personal lifestyles may also collate with the chronic environmental induction in enhancing the number of mutational events. For instance, exposure to pesticides, smoking habit, alcohol consumption, carbonated waters, physical stress, immunity loss, and lack of better nutrients and supplements (anticancer) may play either additive roles or synergistic roles (Indira et al 2015). Perucho et al (1996) are of the opinion that any cancer pronounced in any of the organs show invariably enormous numbers of mutations.

The extensive point mutations have been demonstrated in different types of cancers. (Francis Amirtharaj and our personal observation) have revealed such point mutations in breast cancer patients, cellular mitochondrial genome. Perucho (1996) in his studies on colon cancer using arbitrary primers for PCR amplification detected at different loci of DNA and calculated more than 100000 mutations. The mutations observed by these authors were in the microsatellites, repetitive nucleotide sequences located between genes. In their study revealed that repetitive sequences (mutations) have also occurred within the genes of colonic cancer cells at very high frequencies. These repetitive sequences undergo either contraction or expansion in cancer cells. The above genetic event of repetitive sequences within genes is attributed for inactivation of tumour suppressor genes during tumour progression.

High levels of microsatellite instability are prominent in the hereditary polyposis colon cancers. In these cancers DNA mismatch repair was attributed. In other types of cancer which exhibit expansion or deletion of repetitive sequences, the diminished DNA repair is attributed methylation. (Leung et al 1998). Changes in the length of repetitive sequences are previously considered as the events mediated by the slippage of DNA polymerases.

However, Jackson et al (1998) have opined that oxidative DNA damage could be the direct effect of microsatellite instability. Loeb and Loeb (2000) have revealed damage to plasmid DNA repetitive sequences by ROS which enhanced the DNA polymerases enzyme slippage which in turn enhanced the microsatellite instability. Moreover, Frame Shift changes in microsatellite repetitive sequences by reactive oxygen species was reported to be fold greater than non-repetitive sequences. If such instability in repetitive sequences were to be established by ROS induced change to DNA in cancer cells, the cure for cancer may not be feasible by gene therapy nor by any other genomic devices but only by free radical scanvengers like phytochemical nutrient molecules.

Singh et al (2010) in their study on androgen receptor gene in Indian women with breast cancer, have reported that among 747 breast cancer patients and 661 control individuals the mean CAG report length between cancer cases and controls showed no significant differtences in the variance (Lavenes test for equality of variances). Their studies further revealed that CAG repeat length distribution did not differ significantly between Pre- and Post-menopausal cases of breast cancer women patients. Similar non-association of CAG repeat with breast cancer was noticed among Hispanics, non-Hispanics, cancanrians in Auatralian, Canadians, Israelis, and Spanish populations. (Kadouri et al 2001; Haiman et al 2002; Spurdle et al 2006).

The meta-analysis in different country populations revealed that the CAG repeat length polymorphism may be population specific in causing cancer risk especially the above association in familial groups is also doubtful. Other than CAG repeat length several other factors may be construed to play a role in breast cancer risks. For example, estrogen exposure stress, testosterone levels during menopause, combination of CAG repeat with other repeats like GGC and their polymorphism combination of AA and Vit-D receptor germ line mutations etc.(Wooster et al 1992) have been reported to show the association but dubiously in these studies.

Literature from other studies thus reveal that AR gene may be pleiotropic in function since AR mutations also cause various disorders like gymacomastia, testicular atrophy, Oligo zoospermia or azoospermia, spinal and muscular atrophy etc. Hence it may be premature to conclude the certainty of the CAG repeat polymorphism as a genomic biomarker to breast cancer even in familial groups.

The innumerable reports in the studies of repetitive sequence polymorphism still could not unravel the secrets of such repetitive sequence abnormalities confirmatively to attribute for a disease like breast cancer. This is quite tenable and expected in view of the operation of a plethora of genic mechanisms inside the genome of human individuals. In this context the distribution of i. several hundred copies of reverse transcriptase genes which can reverse transcribe and put back the normal sequence in the place where it is changed. ii. the integration of several thousand viral genomes which remain functional where they are integrated or non-functional when they flip off. iii. the distribution and the random integration of selfish DNA elements and / or jumping gene elements (transposons) which jump in and integrate in the midst of the functional genes and cause mutations as well as jump out and reverse the mutation and make the gene to normal profile, are of interest to mention in their own right.

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