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Does Elevated Alpha-fetoprotein During Pregnancy Protect Against Breast Cancer Later in Life? A Commentary

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Abstract

Elevated maternal serum alpha-fetoprotein (sAFP) has been associated with a future breast cancer risk reduction in previously pregnant women. Past reports have indicated that the presence of high sAFP concentrations in the second and third pregnancy trimester could convey a protective effect against breast cancer later in life. During pregnancy, elevations of sAFP can be attributed to: a) twins and multiple pregnancies; b) fetal defects such as spina bifida and anencephaly; c) gestational hypertension; d) pre-eclampsia; and e) ethnicity. AFP is also elevated in adults with DNA repair diseases such as ataxia telangiectasia and Fanconi anemia. Normally, AFP is a growth enhancing agent; however, a conformationally-altered form of AFP (known as transformed AFP) as well as AFP-derived peptides have been shown to be growth-inhibitory agents. It has further been demonstrated that various third domain AFP short amino acid sequence stretches can bind and interact with mutated and/or misfolded proteins of the cell cycle DNA repair process that erroneously allow replication of cells with damaged DNA. Thus, there appears to be at least three possible mechanisms working singly or in concert that might explain the observed breast cancer risk reduction in later the life of previously pregnant women.

Keywords: Alpha-fetoprotein; Breast cancer; DNA repair; AFP peptides; Cell cycle; Growth suppression; Maternal serum; Chromosome instability

Commentary

Elevated levels of maternal serum alpha-fetoprotein (sAFP) during pregnancy have long been associated with a reduced risk of breast cancer in women later in life. Since the decade of the late 1990's and early 2000's, investigators have reported that elevated sAFP levels during pregnancy were associated with a future reduction in breast cancer risk in both pre-and postmenopausal women. An initial study by Richardson et al., using stored frozen maternal serum samples, reported that a reduced risk of postmenopausal breast cancer was associated with high third trimester sAFP levels in women younger than 28 years at first pregnancy[1,2]. Having been stored for at least 20 years, Richardson re-assayed the frozen/thawed maternal sAFP samples from women with presently confirmed breast cancer. A subsequent report by Danish investigators, using the country of Denmark's national medical records as a resource, confirmed and extended the earlier studies of Richardson to include second trimester sAFP levels in premenopausal women up to age 38 years [3]. A later study by Vatten et al. further confirmed both earlier reports of sAFP and future breast cancer risk and extended their finding to include cord serum AFP, ethnicity, and pre-eclampsia [4,5]. Overall, at least five reports have provided evidence that elevated sAFP levels during second and third trimesters and at term protected women against breast cancer later in life. The protective effect was especially effective at young maternal age of pregnancy.

The breast cancer protective effect of sAFP had been earlier implied in case history reports of elevated AFP-related pregnancy complications encompassing: a) twins and multiple pregnancies; b) fetal defects including spina bifida and anencephaly; c) gestational hypertension; and d) pre-eclampsia [6,7]. All pregnancy conditions or complications shared the commonality of sustained elevated sAFP levels in the second and third trimesters of pregnancy.

Fetal AFP is normally transferred across the placenta and into maternal serum which of course circulates throughout the mother's body. Full-length native AFP is largely a growth enhancing (promoting) protein; however, a small percentage (~10%) of the placental-transpassaged AFP molecules undergo a conformational change which results in a growth inhibitory form known as "transformed AFP" (tAFP) [8,9]. This conformational transformation of AFP has been shown to occur by exposure to excessive concentrations of free long-chain fatty acids (C:20; C:22) and steroids present at the placental interface [10,11]. Inevitably, both native AFP and tAFP will circulate throughout the mother's body and some molecules will come into contact with maternal breast tissues. Thus, it is conceivable that some tAFP molecules could encounter microfoci of breast cancer cells starting to "nest" in breast stromal tissue and initiate growth; tAFP is capable of inducing growth inhibition/suppression in such cancer cells as demonstrated in experimental animal and cell culture models [12,13]. Solitary and isolated cells held in a growth suppressive state for extended periods will eventually succumb to apoptosis. For example, AFP has already been reported to induce programmed such cell death in breast cancer cells undergoing DNA fragmentation and growth arrest [14]. Although the function of the body's immune surveillance cells (lymphocytes, natural killer cells) is to eliminate startup breast cancer microfoci, many such cancer cells have been reported to evade and slip through the lymphocyte surveillance system to escape and survive in situ [15,16]. Moreover, a growth inhibitory site on transformed AFP has been isolated, synthesized, and purified; the site was revealed as a 34 amino acid peptide and termed Growth Inhibitory Peptide (GIP); this AFP-

derived peptide can inhibit and suppress cancer growth including breast malignancies [17-19].

Could there be a further explanation for the breast cancer protective effect involving elevated levels of sAFP? One possible answer may lie in the clinical presentation of the chromosome instability diseases such as Fanconi's anemia (FA) and Ataxia telangiectasia (AT), both known to be DNA repair disorders [20]. Both diseases demonstrate elevated sAFP levels in infants, juveniles, and adults. AT disease exhibits mutations in cell cycle checkpoint kinase enzymes involved in cell cycle arrest and DNA repair. Fanconi anemia (FA), also involved in DNA repair in aberrant cells, can override cell cycle checkpoint arrest allowing cell mitosis to proceed. Thus, damaged or mutated FA proteins are able to bypass the cell cycle G2-to-mitosis checkpoint (CHK1) phase of the cell cycle which permits replication of cells which harbor damaged DNA [21].

It has been demonstrated by both "in silico" (computer) and experimental studies that the third domain amino acid sequence stretches on AFP (AFP-3D) are capable of binding and/or interacting with proteins of the cell cycle DNA damage and repair response [22]. In this prior report, it was shown that certain short amino acid sequences on AFP-3D are capable of interacting with ataxia telangiectasia mutated (ATM) proteins, AT/RAD3 related (ATR) proteins, and Fanconi anemia complementation group (FANC) proteins (i.e., FANCD2). It is the FANCD2 and FANCN1 proteins that are capable of interacting with BRCA1 and BRCA2 proteins forming multi-protein complexes that normally monitor DNA damage during cell cycle progression [23]. However, in the G2 phase of the cell cycle, aberrant FA cells harboring unrepaired damaged DNA are capable of activating checkpoint regulatory protein components and override G2/M transition arrest. Normally, the checkpoint 1 (CHES1) protein will halt cell cycle progression at the G2 phase in the presence of unrepaired DNA; this step prevents damaged DNA cells from replicating [24]. In FA patients, cells containing mutated DNA-repair proteins will allow mitosis to occur, thus, propagating corrupt DNA-containing cells throughout the body including of course breast tissue. As described above, short amino acid sequence stretches from AFP-3D are capable of binding and interacting with DNA-repair proteins of MCF-7 breast cancer cells which are then eliminated by apoptosis. Furthermore, it has been demonstrated that the 34-mer GIP peptide was capable of down-regulating the expression of DNA repair proteins (CHES1, FANCD2) as evidenced by mRNA microarray analysis in cultured MCF-7 breast cancer cells [25,26].

In conclusion, it is tempting to speculate that during pregnancy, AFP and its derived peptides could contribute to the reduction of breast cancer risk in women later in life. It is presently proposed that microfoci clusters of breast cancer cells in pregnant women could be eliminated by three possible mechanisms working singly or in concert. These mechanisms are: 1) growth suppression, inhibition, and elimination of microfoci breast cancer cells by tAFP and/or AFP-derived growth inhibitory peptides; 2) AFP-3D amino acid sequence stretches that bind and interact with maternal breast cancer cells carrying damaged DNA-repair proteins such as ATM, RAD3, BRCA1, BRCA2, and FANCD2; and 3) the AFP-derived growth inhibitory peptide down-regulation of mRNA in DNA-damaged and/or mutated proteins (such as FANCD2 and CHES1) of the DNA-repair system in breast cancer cells. Thus, there are at least three different mechanisms of AFP and its isoforms that might act singly or be additive in reducing future breast cancer risk in previously pregnant women. Unfortunately, it could be predicted that such protection would not be afforded to never-pregnant women or women conceiving late in their reproductive years.

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Interest:

The author declares that there are no known conflicts of interest in the preparation of this manuscript.

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