From: Ed Friedman <ed@math.uchicago.edu>
Subject: **Re: E2 therapy**
Date: August 19, 2009 10:10:01 PM EDT
To: Rebecca Glaser <rglaser@woh.rr.com>

Rebecca,

I wish Danny well at Carnegie Mellon. I was very impressed with him when I met him. You should be proud of the job you did raising him. I have two years before my son Dan starts college. I'm sure it will be hard for us to see him off then too.

You can read my letter in advance of publication at:
http://www.europeanurology.com/article/50302-2838(09)00802-1/fulltext

My model can explain the results of the article you sent me about E2 therapy in a fairly straightforward manner. Ordinarily, there is more ER-beta than ER-alpha so a high enough level of estradiol prevents breast cancer. (For ordinary genetics, I believe that high enough levels of estradiol, progesterone, and testosterone all act to prevent breast cancer - which is why it is so rare in young adult women.) The fact that women have ER+ breast cancer does not negate the fact that the cancer population will be heterogeneous. So when Arimidex is given, those cancer cells that are dependent on ER-alpha will die off and the nature of the overall population will change. Now those cancer cells which need progesterone to increase Bcl-2 or which just naturally have a higher baseline level of Bcl-2 will dominate the population. When E2 is later given, those cells which have higher amounts of ER-beta than ER-alpha will decrease their amount of Bcl-2 and many will die off. Of course, this is not going to cure anyone and the cancer will eventually continue to progress, with the population now switching and consisting mostly of cancer cells with larger amounts of ER-alpha, lots of PRA, mutations that inhibit apoptosis, etc. The key to visualizing all of this is to realize that natural selection will always change the nature of the population to select those that can survive for any given condition. The confusion comes about because many doctors tend to talk about the cancer in terms of Lemarckian evolution instead of Darwinian evolution. So they talk about the cancer first thriving in the presence of E2 and then after Arimidex treatment now magically dying in the presence of E2. If you use Darwinian natural selection things are much easier to visualize - changing conditions usually kills off one part of the cancer population while increasing the rate of growth for other parts of the population. In this case, Arimidex kills off those cells dependent on E2, but has no adverse effect on those cells with higher levels of ER-beta, since so little E2 is present.

Now that I've written this it seems a little more complicated when put in words than the image inside my head. Let me give you analogy of a different hormone to try to explain it better. If you gave a woman with BCa lots of progesterone, you would initially usually see a decrease in tumor size with the BCa cells with lots of PRB dying off. As you continue using progesterone those BCa cells with lots of PRA and little PRB are going to have an enormous selective growth advantage and will start to dominate the population and starve out competing BCa cells. At the point that the BCa is doubling close to as fast as it can, stopping progesterone and switching to RU-486 would kill off those BCa cells dependent on PRA for giving them the Bcl-2 they need to survive. The result would be lots of dead BCa cells, but those cells growing independent of PRA would not be affected and the surviving population would now have totally different characteristics than what the original starting population had.

Ed