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The purpose of the research supported by this IDEA grant award, is to provide the first critical test of the possibility that variability in the strength of immune surveillance mechanisms against caner (operationally defined by assessment of natural killer cell activity) may be a factor in determining the penetrance of mutations in breast cancer susceptibility genes. Two possible explanations for variability in NK cell activity are being investigated: 1) stress-induced immune suppression, and 2) inherited deficits in immune surveillance. This year, we have collected data on an additional 91 women for a total of 184 participants to date. We have requested a no-cost extension of the award anticipating that, on our improved referral rate to the study, we will be able to complete the proposed research during this period.

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INTRODUCTION:

A growing body of evidence strongly supports the view that modifying genes and/or environmental factors may have a major impact on the expression of mutations in breast cancer genes (BRCA1/BRCA2) (Antoniou et al., 2002). We do not yet know the factors responsible for differences in the penetrance of mutations in these primary susceptibility genes (Dite et al., 2000; Antoniou et al., 2002;). Research concerning these putative modifying factors has thus far focused on hormonal/reproductive variables, which have been shown to be risk factors for the development of breast cancer independent of familial risk (deJong et al., 2002; Martin & Weber, 2000). Some risk factors for breast cancer, however, are likely to have an impact only in conjunction with mutations in primary susceptibility genes (Antoniou et al., 2002; Peto, 2002). Such factors might be revealed when examined in conjunction with testing for primary susceptibility genes (deJong et al., 2002). The purpose of the research supported by this IDEA grant award, is to provide the first critical test of possibility that differences in the strength of immune surveillance mechanisms against cancer (operationally defined as natural killer cell activity) may be a factor in determining the penetrance of mutations in breast cancer susceptibility genes.

Two possible explanations for variability in NK cell activity (Bovbjerg & Valdimarsdottir, 2001) are being investigated: 1) stress-induced immune suppression, and 2) inherited deficits in immune surveillance. In addition, we are examining the possibility that inherited deficits in immune surveillance may be independently associated with familial risk of breast cancer (Bovbjerg & Valdimarsdottir, 2001). The study "piggy-backs" on other ongoing studies involving familial risk, genetic counseling, and breast cancer gene testing (BRCA1, BRCA2) at Mount Sinai Medical Center under the direction of Co-Investigators on this proposal. The participants in the present study are recruited to form three Study Groups (N=80/group) of comparable age for the research: 1) The Mutation-Positive Family History Group (Mut+Hist+) includes women whose family histories of cancer indicate a relative risk $\geq$ 1.5 for breast cancer and who carry a mutation in BRCA1 or BRCA2; 2) The Mutation-Negative Risk Family History Group (Mut-Hist+) includes women with comparable family histories, who do not carry mutations; 3) The Normal Risk Group (Mut-Hist-) includes women without family histories of cancer who do not carry mutations. To reduce participant burden, women in the study are asked to complete psychological assessments (e.g., standardized self-report measures) in conjunction with their involvement with the parent studies that fund the genetic testing (e.g., once prior to their genetic counseling session/blood draw and twice after notification). To reduce participant burden and avoid compromising the parent studies, blood samples for the assessment of NK cell activity are also collected in conjunction with the women's involvement in the parent studies, by collecting additional samples when the women are already providing a sample for genetic testing. In the context of the requirements of the parent studies, it has not been feasible to collect blood samples for the two follow-up NK cell assessments originally proposed for this study, as psychological data is collected by telephone. Consistent with scheduling exigencies, NK cell activity is concurrently assessed in samples from women in each group by personnel "blind" to group status.

BODY:

As of this reporting period, we have not yet analyzed data from this study, as our intended sample sizes have yet to be met. As reported previously, we fell behind the proposed rate of study accrual for reasons related to a change in study site from Memorial Sloan-Kettering Cancer Center to The Mount Sinai Medical Center. Having addressed the initial challenges posed by this transition and then subsequent reductions in referral rates at Mount Sinai due to the relocation to another medical school by a critical investigator, and with the strong support of investigators now involved in the "parent" studies that provide the funding for genetic testing, we have made strong progress during this reporting period. This year, psychological assessments of stress associated with familial risk and genetic testing have been conducted with 91 women. Over the grant period a total of 184 women (Mut+Hist+ n=58; Mut-Hist+ n=60; Mut-Hist- n= 66) have completed psychological assessments (Assessment 1: n=184; Assessment

2: n=180; Assessment 3: n=151). This year, NK cell activity has been assessed in blood samples from 57 women. Over the grant period NK cell activity has been assessed in a total of 87 women (Mut+Hist+ n=24; Mut-Hist+ n=26; Mut-Hist- n= 37).

PROPOSAL:

We have requested and have been granted (see memo attached) another no-cost extension of the grant to allow us to address the study aims over the course of the next year. We have three genetic counselors referring potential participants from related studies involving BRCA testing and counseling. Thus, with continued strong referral of potential participants to the study as a result of research and clinical efforts by the current team of Co-investigators, we anticipate no difficulty completing data collection for the psychological assessments (final n=240 proposed) during the next year. For the assessments of NK cell activity, we do not anticipate being able to reach that sample size by the end of the study period. Based on last year's record we anticipate reaching a final n =140. Interpretation of any null findings from analyses of these data will therefore need to include considerations of statistical power. The Hypotheses and Technical Objectives, as well as the basic study design of the research project will remain unchanged from the original peer-reviewed and approved grant.

KEY RESEARCH ACCOMPLISHMENTS:

At this point in the research no results are yet available, but solid progress has been made in recruiting participants to the study and collecting data as proposed in the protocol.

REPORTABLE OUTCOMES:

None at this time.

CONCLUSIONS:

At this point in the research, no results are yet available. If results of the proposed research are consistent with the hypothesis that deficits in immune surveillance (e.g., as a result of stress) moderate the effects of mutations in primary susceptibility genes, the study could have important implications for the eradication of breast cancer. Such results would raise the possibility that appropriate interventions to reduce stress and increase the activity of immune surveillance mechanisms in women carrying mutations in primary susceptibility genes might delay the onset or prevent the development of breast cancer.

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