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Hormonal Determinants of Mammographic Density

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Hormone Replacement Therapy (HRT) has been shown to increase breast cancer risk as well as to increase breast density. Breast density, a reflection of the histologic composition of the breast, is one factor shown to affect mammographic sensitivity and specificity, and it is predictive of breast cancer risk. Thus, the use of HRT, through its effect on breast density, may compromise the well-established reduction in mortality gained by mammographic screening. However, not all women on HRT will experience an increase in breast density. We propose a novel hypothesis to explain in part the individual variability in breast density seen among women on HRT: differences in breast density are associated with differences in estrogen metabolism, and this association may be attenuated by individual factors such as body mass index and HRT regimen. Our work and the work of others provide compelling evidence to support this hypothesis.
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Introduction
The specific objective of this proposal is to begin to understand factors associated with individual variability in breast density including HRT, BMI and estrogen metabolism. Our rationale is that by understanding factors that affect breast density, we can improve breast cancer screening as well as to identify women at an increased risk of breast cancer. We will accomplish this objective by pursuing the following specific aim: to determine the effects of serum markers of estrogen metabolism, body mass index (BMI), and hormone replacement therapy (HRT) on postmenopausal breast density. This is an observational study within an ongoing study of the relationship between HRT, estrogen metabolism and breast cancer (PA State 2777693, Modugno, PI). We will measure estrogen metabolite levels and mammographic density in a group of 300 postmenopausal women (150 HRT users, 150 non-users), and correlate metabolite levels with qualitative and quantitative measures of breast density.

Body
Work Plan: Research Proposal

We currently have 175 women recruited from the Magee-Womens Hospital system. Recruiting women currently on hormone replacement therapy (HRT) has been an issue since the release of the Women’s Health Initiative (WHI) report of the increased incidence of breast cancer related to estrogen + progesterone combination HRT. We continue to focus on recruitment of women from the Magee-Womens Hospital system and will attempt to recruit those women still taking HRT to ensure that we have adequate representation of non-users, estrogen only, and estrogen + progesterone users. For those women recruited, blood has been processed and stored, mammographic films have been collected and a take home questionnaire was given to each subject. The database has been constructed and each subject's data was key entered twice. After receipt of the questionnaire, it is reviewed for any discrepancies or blanks. If needed, the subject is called for clarification. After the first key entry, a set of edit checks were run to identify data entry errors as well as inconsistent responses. The edit checks were then addressed and a second key entry is performed. Finally, the two data sets are compared and reconciled. To date all 175 subjects’ data has been entered and cleaned. As our main concern was lack of HRT use among subjects, an initial query of the database reveals approximately 42% of women were on HRT at the time of enrollment. Further analysis of the database is currently in progress.

An initial sample of buffy coat was sent to Dr. Ferrell and serum to Immuna Care for quality check. Both sets of samples were acceptable. Of the 175 samples we have currently sent 31 to Immuna Care for estrogen metabolism testing. With the exception of 2, due to low volume, all samples were sent with blinded duplicates to check reproducibility of the 2- and 16-OH assays. Coefficients of variation were all less than 15%. We are currently in the process of preparing the next shipment to include the remaining serum samples. All samples are given random numbers and are placed in a randomly generated order in the box to ensure that the processing of the samples is blinded. Additionally, we have just sent all current subject mammographic films (N=175) to Ms. Martine Salane for breast density reading. Results are pending at present and will be entered into the database upon receipt.
Work Plan: Training Proposal
In addition to required coursework, I have taken an additional course in Nonparametric statistics in preparation for the statistical analyses that will be required for this project data set. Once results are available on the initial 175 subjects, an abstract will be prepared for submission to AACR. As outlined, I have attended the weekly Cancer Prevention Journal Club to discuss topics in cancer prevention, gain experience in presenting research results, and practice presentations for national meetings as well as for preparation for my defense presentation. Additionally, I have attended the annual UPCI retreat to learn about ongoing research within the university environment and those clinical grand rounds that focus on breast cancer.

Key Research Accomplishments
- Initiated Recruitment in the Magee-Womens Hospital System
- Serum and buffy coat sent for quality check - samples acceptable for analysis
- Initial batch of mammographic films sent for breast density reading
- Database constructed
- Data to date has been entered and cleaned
- Study remains in progress at current time

Reportable Outcomes
None to date

Conclusions
N/A – study in progress

References
References


64. Colditz GA Relationship between estrogen levels, use of hormone replacement therapy, and breast cancer. Journal of the National Cancer Institute, 87: 190-197, 1998.


