February 7, 2003

Matching Results for Ancillary Study #134:
Serum estrogen Hormone Metabolites, Hormone Replacement Therapy and the Risk of Breast Cancer

Case / Control Selection:

All centrally adjudicated cases of incident invasive breast cancer were selected as cases from the August 31, 2002 database from the WHI Observational Study. Along with being centrally adjudicated, all prospective cases also needed a completed estrogen and progesterone receptor assay data on Form 130. This left a total of 1,658 potential cases (out of an original 1,918) and 91,654 potential controls.

Potential cases and controls were excluded if they possessed any of the following characteristics:

Breast Cancer Diagnosis Less Than Five Years Past Menopause (Cases Only)
Inadequate Baseline Serum Supply
Any Locally Adjudicated Other Incident Cancers (Including Breast Cancer for Controls)
Any Self-Reported Cancer prior to or at Baseline
Reported Other/Unknown Ethnicity
Any use of the following Medications Reported at Baseline or AV-3:

Antimycobacterial Group (i.e. Rifapentine)
Imidazole-Related Anti-Fungals Group (i.e. Ketoconazole)
Androgen-Anabolic Group (i.e. Testosterone)
Adrenal Steroid Inhibitors Group (i.e. Aminoglutethimide)
Hormone Receptor Modulators Group (i.e. SERMS)
H-2 Antagonists Group (i.e. Cimetidine)
Cyclosporin Analogs (i.e. Cyclosporine)
Herbal Estrogens (i.e. dong quai)

In addition to these restrictions, potential cases and controls were also restricted to specific methods of hormone use. To meet this restrictions, participants either had to have no hormone use of any kind (as reported on Form 43 and confirmed by Baseline and AV-3 Medications) or be current users at baseline (for at least one year) of Conjugated Equine Estrogen pills, with or without Progesterone pills (as reported on Form 43). A summary of these restrictions is as follows:

Hormone Group	***Requirements***

Non HRT Users	No Use of Hormones in Any Form Reported on Form 43
	No Use of Hormones as Reported by Current Medications at Baseline & AV-3
Current Estrogen Users	Current CEE Use for at Least One Year (Form 43)
	No Non-CEE Hormone Use in the Past Year as Reported on Form 43
	Daily Estrogen Use
	No Progesterone Use within 4 years of Baseline (Form 43) and No Progesterone Use Reported on Baseline and AV-3 Current Medications
Current Estrogen + Progesterone Users	Current CEE + Progesterone Use for at Least One Year (Form 43)
	No Non-CEE Hormone Use in the Past Year as Reported on Form 43
	Daily Estrogen Use
	Continuous (Reported use of at least 25 days / month OR Prempro Every Day) or Cyclic ((Reported use between 7-16 days per month AND reported interval of use Between 5-18 days per month) OR Premphase user) Progesterone Use

Current users of CEE's were defined as those participants who listed a CEE stopping age that was the same as their age of filling out Form 43 (actual dates of use were not collected). This makes it possible for some participants listed as current users to have actually stopped using CEE's up to one year prior to their filling out of Form 43. Participants in the CEE category were not allowed to be on any estrogen or progesterone creams, shots, or implants and remain eligible. Non-hormone users were required to have never had hormone use of any kind, including shots, pills, patches, creams, and implants with either estrogen and/or progesterone.

Out of an original 1,658 cases and 91,654 controls, a total of 1,161 cases and 62,919 controls were excluded from the prospective case / control set using the above criteria, leaving a total of 497 invasive breast cancer cases (292 Current CEE Users; 205 Non HRT Users) and 28,735 controls (12,577 Current CEE Users; 16,158 Non HRT Users).

Matching criteria:

Matching is done on number of years from age at menopause to study entry (within 1 year), ethnicity, randomization clinic, CEE use (at least one year's use at baseline, never use), type of HRT (with or without Progesterone), and enrollment date (within 1 year). Ethnicity, randomization clinic, CEE use, and type of HRT (the categorical variables) were matched exactly, and the remaining continuous matching variables were selected based on criteria to minimize an overall distance measure (Bergstralh EJ, Kosanke JL. Computerized matching of cases to controls. Technical Report #56, Department of Health Sciences Research, Mayo Clinic, Rochester, MN. April 1995). Matching was done in a time forward manner to ensure that each control had at least as much control time as its matched case. For example, a case diagnosed with

breast cancer two years after randomization would be matched with a control with at least two years of follow-up. SAS code is available to implement this matching scheme.

Matching summary:

A total of 497 incident cases of invasive breast cancer and 28,735 controls were put into the matching process. 468 cases were successfully matched with controls (29 unmatchable cases). A sample of 100 CEE Current User matches and 100 HRT Non-Users were selected for the study population via simple random sampling, giving a total of 200 case / control pairs.

Specific matching summaries are given in the tables below. Each row summarizes the matching performance for a specific variable or overall criteria. For example, the mean case-control absolute difference in enrollment date is 0.20 years (73.1 days), with a maximum difference of almost a year. The mean enrollment dates in the case and control groups are September 26th and September 27th, 1996, respectively. The mean case-control absolute difference in years from menopause to study entry is .14 (51.1 days). The 'overall' measurement represents the total of absolute deviations for all matching components. Thus, an overall average difference of 0.34 means that the total difference in the enrollment date plus the total difference in years from menopause to study entry averages to 0.34. The weighting equates a deviation of one year in enrollment date to a deviation of one year in the time between menopause and study entry. Ethnicity, randomization clinic, HRT use, and HRT type are matched exactly for all subjects.

Balance on each covariate individually and overall is sufficient.

Matching Factor	Sum (weighted) of Absolute Differences	Cases	Controls
	Mean (min, max)	Mean	Mean
Overall	0.34 (0, 1.56)	-	-
Ethnicity	0	-	-
Randomization Clinic	0	-	-
HRT Use (Current or Never)	0	50% Current	
HRT Type (with or without Prog.)	0	60% PERT	
Enrollment Date (years)	0.20 (0 , 0.99)	9 / 26 / 96	9 / 27 / 96
Menopause to Study Entry (years)	0.14 (0 , 1.00)	15.51	15.52