Massive Nurses' Health Study, in Seventh Year, Reports First Findings on Disease Links in Women

Boston, Mass.

Looking for answers to cancer and cardiovascular disease, more than 100,000 nurses joined Harvard researchers in 1976 in an extraordinary long-range study of health risks that pose a special threat to women. Seven years into the study, the research team is ready to make some preliminary conjectures about the health effects of smoking, hair dyes, and oral contraceptives. The first long-term analyses of data from the study will be published by the end of this year.

The Nurses' Health Study was inspired by concerns that long-term use of birth-control pills might lead to cancer and myocardial infarction. The study's scope has expanded steadily from that point: With more than 120,000 nurses responding, investigators decided to assess the effects of cigarette smoking and hair dyes. Then participants proposed that diet and other factors be explored.

By now, the nurses are also supplying information on lifestyle, stress, use of prescription drugs, disease diagnoses including lung, colon, ovarian, uterine and bladder cancer and melanoma, cardiovascular and cerebrovascular events, diabetes, rheumatoid arthritis and fractures. In one of its best-publicized projects, the team is collecting nurses' nail clippings to see whether dietary intake of selenium affects cancer rates.

The NIH-funded study is unique in the breadth and depth of its focus on women's health. And no other study relies on nurses exclusively.

Nurses were singled out, according to principal investigator Frank Speizer, because the study called for "a sophisticated group of individuals who could report exposures and diseases more accurately than the general population." Thus, the researchers can take information directly from questionnaires instead of interviewing women individually, making the NHS "highly efficient," says Dr. Speizer.

The population under study is made up of married, female registered nurses born between Jan. 1, 1921, and Dec. 31, 1946, and residing in 11 states with the largest number of RNs: New York, California, Pennsylvania, Ohio, Massachusetts, New Jersey, Michigan, Texas, Florida, Connecticut and Maryland. Participants were recruited from a group of 238,026 eligible RNs who received the initial study questionnaire in 1976. More than 70 percent responded.

The project has enlisted the efforts of a considerable number of faculty members and doctoral students at Harvard Medical School and School of Public Health. Working with the study team on analyzing the smoking data is Ann Hall Harvey, an assistant professor of graduate medical-surgical nursing at the University of Maryland, who is currently completing her doctoral dissertation on that aspect of the study.

The study operates by sending a detailed questionnaire every second year to all 122,000 RNs. In addition to answering a battery of questions, nurses are asked to report any diseases diagnosed during the two-year period. Returns, identified by number only, are coded into computer systems. All forms and any notes enclosed are also reviewed individually.

When disease diagnoses are reported, investigators write for the nurse's permission to obtain the medical records or discharge summaries. RNs have been "highly cooperative" with this phase of the study, says Dr. Speizer.

With continued funding from NIH, the study is expected to make some breakthroughs in areas that have been relatively neglected. Diet, for instance: though measurement of dietary "exposures" presents some formidable problems, the Harvard team tackled it in 1980. All women in the Nurses' Health Study were mailed a list of 70 foods and were asked to report how often (on a scale ranging from "never" to "six or more times a day") they had eaten each food during the preceding year. The nurses were then ranked in groups



The Nurses' Health Study Group: (seated, left to right) Walter C. Willett, Frank E. Speizer, Barbara Egan. (Standing) Meryl Dannenberg, David Dysert, Sarolta Petro, Graham Colditz, Charles Hennekens, Marilyn Bell. Not pictured: Christopher Bain, Rosa Bova, Robert Lipnick, Bernie Rosner, Laura Sampson.

of high, medium and low intake for each food.

To check the accuracy of the findings, the project enlisted 200 Boston-area nurses who carefully weighed and recorded their daily food intake for four one-week periods spaced over a year. The women also provided blood specimens so that their actual blood levels of vitamin E, carotene and lipids could be compared with the intakes reported.

Dietary data will be used to interpret disease rates experienced by women with different levels of nutrient intake. By next year, says Project Director Walter Willett, there will be data relating to breast cancer. By 1987 he expects to be able to find correlations between diet and cardiovascular disease as well as cancer of the lung, colon and endometrium.

The massive pursuit of toenail clippings was undertaken on the hypothesis that selenium protects against cancer. Investigators collected nail clippings from people living in four areas and found, as they suspected, that selenium levels in toenails reflect daily intake and absorption. So all study participants were asked to contribute their nail clippings to science. So far, the nurses have mailed in over 50,000 sets.

Dr. Willett and his colleagues will also use the nails to measure other trace elements in diet. Over time, they will pair women who develop certain diseases with those who don't. They view this phase of the project as a first step toward the development of biological "markers" of exposure to disease.

Another outcome: The research group was surprised to find that nurses are heavy users of vitamins. A pilot study revealed that 25 percent were megadosing on vitamin C, 15 percent were taking high doses of vitamin E, and 38 percent were taking multiple vitamins. "If there is really any health benefit of taking megadoses of vitamin supplements, the Nurses' Health Study should be able to detect it," says Dr. Willett.□

Preliminary Findings of the NHS Confirm and Confound Hypotheses

When the Nurses' Health Study was launched with a 1976 survey, many RNs who agreed to join the project had already made some tacit decisions about exposure to health risks.

Asked to report on their present and past use of oral contraceptives, for instance, 43 percent said that they used to use them, but only 5.5 percent were still using them at the time of the survey. On the other hand, the proportion of cigarette smokers had gone from 24.3 percent before 1976 to 34.5 percent at survey time. Over the same time span, the group who used hair dyes increased from 12.2 percent to 25.3 percent.

The nurses' reports on these exposures have been extensively analyzed. Seeking links between exposure and disease, the team has arrived at some preliminary conclusions.

Causes of breast cancer. About 1 percent of the nurses had already had a diagnosis of breast cancer when they joined the project. The study confirmed that risk was increased for those with a history of benign breast disease and for those whose mothers and sisters had had breast cancer. As other studies have found, women who have an earlier term pregnancy are less likely to experience breast cancer than those whose first pregnancy is late and those who have never been pregnant.

Hair dyes and cancer. Analysis showed little if any excess rate of cancer of any type when hair dyes were used for less than 20 years. The effects of longer use will be assessed as the study continues.

Oral contraceptives. To date, no significant risk is seen between past use of oral contraceptives and the development of ovarian cancer or malignant melanoma. In fact, women using OCs reported slightly fewer cases of ovarian cancer and about the same rate of melanoma as those who never used OCs. However, a higher rate of cardiovascular disease was experienced by OC users over 30 years of age.

Causes of myocardial infarction. Consistent with other studies, the researchers noted an overall increased risk for over-30 users of OCs, for women who smoked and for those with hypertension, diabetes or angina. Early menopause—particularly if both ovaries were removed—was also found to be a risk factor for MI.

Smoking and MI. For smokers, the risk of MI was triple that of women who never smoked. But those who had quit smoking were apparently at no greater risk than those who never smoked at all.

Estrogen supplements. Investigation revealed no excess risk of MI among users. It appeared, in fact, that women who had both ovaries removed were less likely to experience a nonfatal MI if they were taking estrogens.

Since the base data for the study were collected in 1976, the 121,000 participants have reported about 125–150 new breast cancers and 40–50 diagnoses of MI each year. With returns from the 1982 questionnaire, researchers now have enough new data to address their original concerns about the long-term consequences of using oral contraceptives and menopausal estrogens. A preliminary analysis of oral contraceptives and breast cancer is due to be published within a year's time.