Table 1.—Minimal Samples Required to Detect Differences in Disease Rates Between OC Users and Controls in Prospective Study*

Disease	No. of Years After Onset of Study	Annual Incidence Rate in Controls per 10,000	Persons Required in Each Group: Incidence Two Times in OC Users	Persons Required in Each Group: Incidence Five Times in OC Users
Cancer of the breast	1	2.2	85,000	11,000
Cancer of the corpus uteri	1	0.3	600,000	80,000
Cancer of the cervix	1	3.1	60,000	7,500
Cancer of the breast	10	7.5	25,000	3,000
Cancer of the corpus uteri	10	1.3	140,000	20,000
Cancer of the cervix	10	5.6	35,000	5,000
Diabetes	1	20	9,000	1,200
Malformations	1	300	600	100
Thromboemboli	1	20	9,000	1,200

*OC = oral contraceptive. It is assumed that this is a simple random sample of "ever users" of ages between 20 and 45 years. Sample sizes for malformations are for births. The Table is computed for one-tailed significance tests at 0.05 level with power equal to 0.8.

Prospective Studies

Since the incidence rates of the principal problems related to the use of oral contraceptives (thromboembolic disorders, cancer, metabolic changes, and congenital malformations) are low, large populations are required to study them prospectively. In order to establish sample size requirements we must estimate (1) the incidence rate of the disease in control populations, (2) the increase in the incidence rate for groups using an oral contraceptive that is regarded as important to detect, (3) the extent to which the study should be powerful enough to detect such an increase (this power is expressed as the probability of obtainiing statistically significant results, when a real difference exists), and (4) the level of the significance tests. Sample sizes increase as the incidence rates decrease, as the presumed effect of the pill decreases, as the significance levels decrease, and as the power increases. The choice of a particular set of levels for these elements depends on the social and scientific importance of the question, the prior information on the hypotheses at issue, the funds and resources available, and a number of ill-defined personality characteristics in the epidemiologic investigator.

Table 1 provides some sample sizes that are required to detect increases of two times or five times in the incidence of selected cancers, thromboembolism, diabetes, and malformation. It is assumed that the study group in each case consists of women who have ever used the drugs, that the control group is of equal size, and that both are composed of women entering a prospective study at ages between 20 to 45 years. The distribution by age in both groups is assumed to be similar to a representative sample of "ever-users," with a disproportionate number of younger women. Since the incidence rates are computed on the basis of this younger age distribution, they will be lower than would normally be seen for women aged 20 to 45. Rates are those that would be expected for the control cases in the first year of follow-up and ten years later.

For instance, a truly large sample of users, 600,000, and an equal number of controls is required to study endometrial carcinoma in the first year of observation. This hypothesis would be a reasonable one only if members of the study sample had already been exposed to medication for a substantial number of years, since carcinogens characteristically have a long latent period. The other two cancer sites require smaller samples since their incidence rates are larger.

Ten years after such a study is initiated, the ages will range from 35 to 55, and the expected incidence rates will be somewhat higher, so that smaller samples are needed. Even so, 25,000 would be required to study cancer of the breast, assuming there was a doubling in risk.

Detailed data are not available on the incidence rates for thromboembolic disorders. In a review of the epidemiology of such conditions[13] Schuman discussed the deficiency of data on morbidity and tabulated some reported studies that show a ten-fold range in annual incidence of phlebitis and thrombophlebitis. The estimate of this incidence provided in Table 1, 20 per 10,000, is regarded as a rough approximation. It is similar to the experience reported by the College of General Practitioners, 2.4 per 1,000, which was observed in general practice, and consisted largely of women who were treated for superficial phlebitis of the legs.[7] Sample size requirements are considerably smaller than those for cancer, with little more than 1,000 needed where an increase in the incidence of five times is expected. Estimates of the incidence of diabetes are also difficult to obtain.[14] Judging from what is known about the prevalence and the survivorship[15] though, an incidence rate similar to that for thromboembolic disorders is likely, so that the same sample sizes are required.

The estimates for malformations pertain to births from women who have used the oral contraceptive either prior to or in some cases after the conception. Incidence rates are much greater, and sample sizes are below 1,000.

Roughly speaking, the number of persons required for these studies varies inversely with the number of years of follow-up. That is to say, two years follow-up on 1,000 persons gives approximately the same information as 2,000 persons observed for one year. The conditions under which this kind of substitution of person years for persons can be made is still being studied[16] and special care is required in the interpretation of analyses based on person-year data.

All of the sample sizes must be increased to compensate for losses to follow-up, and the increase should be roughly equal to the average number lost