

CANCER RISK AFTER EVALUATION FOR INFERTILITY

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To evaluate cancer risk by various causes of infertility, the authors conducted a retrospective cohort study among 2,335 women evaluated for infertility at the Mayo Clinic between 1935 and 1964. Most cancers occurred at expected frequencies, with the exception of cancers of the thyroid (standardized incidence ratio (SIR) = 2.6) and other endocrine glands (SIR = 6.7), although analyses were based on small numbers. Patients with progesterone deficiencies (31 per cent of the study subjects) had a 20 per cent higher cancer risk than did those with other causes of infertility, with excesses deriving primarily from cancers of the lung, cervix, ovary, and thyroid and from melanoma. Breast cancer risk, however, was not elevated in either patients with progesterone deficiencies (SIR = 0.9) or patients with other causes of infertility (SIR = 1.0). Examination of other parameters of infertility, including age at evaluation, type of infertility (primary vs. secondary), and years of attempted conception, showed no elevated risks of breast cancer in any subgroup. These results fail to support previous studies that have linked progesterone deficiencies among infertile women to elevated breast cancer risk. However, the data suggest a possible involvement of a progesterone deficiency in the etiology of other cancers, particularly thyroid cancer and melanoma.

breast neoplasms; infertility; neoplasms; risk

Nulliparous women and those with late ages at first birth have an increased risk of breast cancer (1, 2). Nulliparity is also a risk factor for cancers of the ovary (3-5) and endometrium (6-9), with multiple

pregnancies or births providing protection. However, the question of whether these associations are due to voluntary or involuntary delays in childbearing remains unresolved. Married, childless women are at higher risk of ovarian (5, 10) and endometrial (8, 11) cancers than single women, and several case-control studies (12, 13) have found an increased risk of these cancers with a history of infertility or related conditions. The nature of the relations is not well established, and the effect of infertility on the risk of breast cancer is even less clear (14), despite hypotheses that anovulation and inadequate corpus luteum function may provide a favorable environment for carcinogenesis (15, 16).

Recently, several cohort studies have been conducted to evaluate whether pa-

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Abbreviation: SIR, standardized incidence ratio.

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tients who experience reproductive difficulties are at increased risk of subsequent cancer and, if so, whether this relates to a specific cause of infertility. Cowan et al. (17), in a follow-up study of 1,083 women evaluated for infertility, found a fivefold increased risk of premenopausal breast cancer among women with endogenous progesterone deficiencies compared with women with nonhormonal causes of infertility. Ron et al. (18), in an analysis of 2,624 Israeli women, found only a moderately increased risk of breast cancer for women with disorders causing unopposed estrogen production, but a 10-fold excess risk of endometrial cancer. In addition, melanoma risk was elevated among women with hormonal infertility, while women with other causes of infertility had excess risks of cancers of the ovary and thyroid.

To study cancer risk among infertile women, we conducted a retrospective cohort study among women evaluated for infertility at the Mayo Clinic between 1935 and 1964. The relatively large size of the study population and the extended follow-up enabled us to evaluate risk in relation to a number of specific cancer sites. In addition, attempts were made to classify the reasons for infertility and, specifically, to examine whether women with progesterone deficiencies were at unusual risk.

MATERIALS AND METHODS

We assembled the study cohort by identifying women diagnosed with infertility at the Mayo Clinic. The diagnosis was made either during an outpatient clinic or office visit or during hospitalization at one of the Mayo Clinic's two large affiliated hospitals. "Infertility" was defined as failure to conceive despite attempted pregnancy without contraception for at least one year. Study subjects were restricted to women first evaluated prior to the age of 40 years; both those with primary infertility (no prior pregnancies) and those with secondary infertility were included. Women included for study were Olmsted County, Minnesota, residents evaluated between 1935 and 1964,

as well as referral patients from neighboring areas (other locales in Minnesota and residents of other states) evaluated between 1950 and 1964.

The original, complete (inpatient and outpatient) medical records for each study subject were retrieved and reviewed. Data, collected on a precoded abstract, included background information (age, race, marital history, alcohol consumption, and cigarette smoking), details of the infertility evaluation, reproductive and medical histories prior to first evaluation, diagnostic tests performed for the evaluation, infertility treatment details, and subsequent events (pregnancies, breast biopsies, gynecologic surgery, hormone use, and development of cancer). Details of the infertility evaluation included information on reproductive tract abnormalities, endometriosis, and thyroid disease, along with results of basal body temperature tests, endometrial biopsies, culdoscopies, Rubin's tests, hysterosalpingograms, Sims-Huhner tests, semen analyses, and diagnostic sella turcica tests. Detailed hormonal evaluations were unavailable because they were not part of the diagnostic tests performed at the time of patient accrual. On the basis of available test findings, one of us (G. D. M.) developed a clinical impression and assigned to each patient one or more of the following causes of infertility: 1) luteal phase defect (inadequate luteal phase or deficient progesterone), 2) polycystic ovary syndrome, 3) oligoovulation or anovulation, 4) pituitary dysfunction, 5) metabolic disorder (thyroid disease, diabetes, or adrenal dysfunction), 6) structural defect (vaginal absence, bicornuate uterus, unicornuate uterus, cervical incompetence, fibroids, septate uterus, or tubal adhesions), 7) male factor (oligospermia, azoospermia, or impotence), and 8) other causes. The assignment of patients to either the luteal phase defect group or the oligoovulation/anovulation group was largely dependent on the absence of either a secretory phase from endometrial biopsies or ovulatory curves from basal body temperature tests. Menstrual histories were

also considered in the classification of patients to the oligoovulation/anovulation group. Patients with luteal phase defects, polycystic ovary syndrome, or oligoovulation/anovulation were considered in this study to have progesterone deficiencies.

Information on the development of cancer was determined by reviewing the medical records for all visits subsequent to the first infertility evaluation. For deceased subjects, copies of death certificates were obtained and information on cancers was abstracted. In addition, we mailed a short questionnaire to all study subjects who had last been seen at the Mayo Clinic prior to the end of the follow-up period (September 30, 1981) to ascertain information on events occurring subsequent to their last visit, including cancer diagnoses, pregnancy, breast biopsies, gynecologic surgery, cessation of menses, and use of female hormones. A total of 6 per cent of the subjects were deceased, 18 per cent were seen at the Mayo Clinic through the end of the follow-up period, and 43 per cent responded to the questionnaire, leaving 33 per cent for whom complete cancer incidence was unknown. This latter figure was less for the Olmsted County patients (21 per cent) than for the referral patients (45 per cent) but did not differ appreciably by cause of infertility (e.g., progesterone deficiency vs. other). In the total series, 60 per cent of the cancers were identified through medical record review, 13 per cent from questionnaire data, and 27 per cent from death certificate information.

Standard cohort analyses were used (19), accruing women-years of follow-up from the time of first evaluation for infertility at the Mayo Clinic until the time of first cancer diagnosis (nonmelanotic skin cancers excluded), death, loss to follow-up, or end of the follow-up period, whichever came first. To compute expected numbers of cancers, we used age-, sex-, and calendar year-specific incidence rates from the Connecticut Cancer Registry. Although Olmsted County rates were available, they were not sufficiently stable for the time-specific

analyses used. Stability of rates also determined the choice of an external standard rather than derivation of expected values using internally derived incidence rates, although for selected analyses we used internal comparisons. Standardized incidence ratios, the ratio of observed to expected events, and 95 per cent confidence intervals for these ratios were calculated.

Selected analyses considered the influence of potential cancer risk factors, for example, age at first live birth. These analyses included only those women for whom complete information was available from either the medical record or the questionnaire. For time-dependent exposures, such as menopausal status, women-years were contributed to each category only until a change in status, with the status of cases being that at their time of diagnosis.

RESULTS

Of the 2,335 study subjects, nearly one half (1,157) were residents of Olmsted County, while the remainder (1,178) were referral patients (table 1). Since the resident patients entered the study, on average, earlier than the referral patients (1950.8 vs. 1956.0), it was possible to follow them for longer periods of time (24.4 vs. 14.5 years) and to accrue more women-years of follow-up. The longer follow-up time for the resident patients also reflected a slightly younger age at entry for the resident patients (27.8 years) than for the referral patients (29.5 years).

A comparison of the traced subjects with those lost to follow-up showed no significant differences with respect to a number of variables assessed at first infertility evaluation, including race, number of marriages, height, weight, age at menarche, menstrual irregularity, number of pregnancies, previous dilation and curettage, gynecologic operations, endometriosis, or use of exogenous hormones. However, those lost to follow-up tended more often to be smokers or alcohol drinkers, had attempted to conceive for longer periods of time, and had more frequent histories of pelvic inflam-

TABLE 1
Characteristics of women evaluated for infertility at the Mayo Clinic, 1935-1964

| | Olmsted County residents (1935-1964) | Referral patients (1950-1964) | All study subjects |
|--------------------------------------|---|----------------------------------|--------------------|
| No. of women identified | 1,157 | 1,178 | 2,335 |
| Women-years of follow-up | 28,264 | 17,144 | 45,408 |
| Mean years of follow-up | 24.4 | 14.5 | 19.4 |
| Mean age (years) at study entry | 27.8 | 29.5 | 28.6 |
| Mean year of study entry | 1950.8 | 1956.0 | 1953.4 |
| Mean age (years) at cancer diagnosis | 51.8 | 48.6 | 50.7 |

TABLE 2
Observed and expected numbers of cases and standardized incidence ratios (SIR) for all cancers and for selected cancer sites among women evaluated for infertility at the Mayo Clinic, 1935-1964

| | Olmsted County residents (WY* = 28,264) | | | Referral patients (WY = 17,144) | | | All study subjects (WY = 45,408) | | |
|-------------------------|--|----------|--------|------------------------------------|----------|-------|-------------------------------------|----------|------|
| | Observed | Expected | SIR | Observed | Expected | SIR | Observed | Expected | SIR |
| All cancers | 98 | 94.90 | 1.03 | 49 | 51.87 | 0.94 | 147 | 146.77 | 1.00 |
| Buccal cavity | 2 | 1.89 | 1.06 | 2 | 1.08 | 1.86 | 4 | 2.97 | 1.35 |
| Stomach | 1 | 1.64 | 0.61 | 1 | 0.66 | 1.51 | 2 | 2.31 | 0.87 |
| Colorectal | 11 | 11.84 | 0.93 | 6 | 4.94 | 1.21 | 17 | 16.78 | 1.01 |
| Biliary passages, liver | 1 | 0.85 | 1.17 | 1 | 0.31 | 3.20 | 2 | 1.17 | 1.71 |
| Lung | 9 | 6.11 | 1.47 | 3 | 3.51 | 0.86 | 12 | 9.61 | 1.25 |
| Bone | 2 | 0.16 | 12.78† | 0 | 0.08 | 0.00 | 2 | 0.24 | 8.41 |
| Melanoma | 2 | 2.05 | 0.98 | 2 | 1.44 | 1.39 | 4 | 3.49 | 1.15 |
| Breast | 37 | 32.36 | 1.14 | 12 | 19.60 | 0.61 | 49 | 51.96 | 0.94 |
| Cervix | 6 | 5.52 | 1.09 | 2 | 3.09 | 0.65 | 8 | 8.61 | 0.93 |
| Endometrium | 6 | 8.25 | 0.73 | 5 | 4.50 | 1.11 | 11 | 12.75 | 0.86 |
| Ovary | 7 | 5.50 | 1.27 | 4 | 3.10 | 1.29 | 11 | 8.61 | 1.28 |
| Other female genital | 0 | 0.61 | 0.00 | 1 | 0.29 | 3.46 | 1 | 0.90 | 1.11 |
| Bladder | 3 | 1.67 | 1.79 | 0 | 0.83 | 0.00 | 3 | 2.50 | 1.20 |
| Brain | 0 | 1.45 | 0.00 | 1 | 0.80 | 1.25 | 1 | 2.25 | 0.44 |
| Thyroid | 4 | 1.37 | 2.92 | 2 | 0.94 | 2.13 | 6 | 2.31 | 2.60 |
| Other endocrine glands | 0 | 0.09 | 0.00 | 1 | 0.06 | 17.38 | 1 | 0.15 | 6.73 |
| Other ill-defined sites | 3 | 2.71 | 1.11 | 1 | 1.24 | 0.81 | 4 | 3.95 | 1.01 |
| Lymphoma | 3 | 3.77 | 0.80 | 4 | 1.96 | 2.04 | 7 | 5.73 | 1.22 |
| Leukemia | 1 | 1.67 | 0.60 | 1 | 0.83 | 1.20 | 2 | 2.50 | 0.80 |

* WY, women-years of follow-up.

† 95 per cent confidence interval 1.4-46.1.

matory disease, venereal disease, uterine abnormalities, and thyroid disease.

Table 2 shows that the observed number of cancers of all sites was nearly identical to that expected for all study subjects together, as well as for Olmsted County residents and referral patients separately. The only significantly elevated risk was for bone cancer among the resident patients (standardized incidence ratio (SIR) = 12.8), but this estimate was based on only two ob-

served cases. Otherwise, overall risks were substantially elevated only for thyroid cancer (SIR = 2.6) and cancers of other endocrine glands (SIR = 6.7), on the basis of one observed cancer of the adrenal gland. With the small number of cases involved, these findings might have occurred by chance alone. For the cancers with the largest number of observed events, there were no significant deviations from expectation, including cancers of the colon and rectum

(SIR = 1.0, 95 per cent confidence interval (CI) 0.6–1.6), lung (SIR = 1.2, 95 per cent CI 0.6–2.2), breast (SIR = 0.9, 95 per cent CI 0.7–1.2), cervix (SIR = 0.9, 95 per cent CI 0.4–1.8), endometrium (SIR = 0.9, 95 per cent CI 0.4–1.5), and ovary (SIR = 1.3, 95 per cent CI 0.6–2.4). Standardized incidence ratios were lower among the resident patients than among the referral patients for lymphoma (0.8 vs. 2.0), while higher standardized incidence ratios were observed among the resident patients for cancers of the lung (1.5 vs. 0.9), breast (1.1 vs. 0.6), cervix (1.1 vs. 0.6), and thyroid (2.9 vs. 2.1).

A total of 728 (31 per cent) of the subjects were classified as having progesterone deficiencies compared with 1,607 (69 per cent) with other causes of infertility (table 3). The standardized incidence ratio for all cancers was slightly higher among the progesterone deficiency group than among the group with other causes of infertility (1.2 vs. 0.9). Higher but non-statistically significant risks were seen among the progesterone deficiency patients compared with the other subjects for cancers of the lung (SIR = 2.3 vs. 0.6), cervix (SIR = 1.3 vs. 0.7), ovary (SIR = 1.6 vs. 1.1), and thyroid (SIR = 5.2 vs. 1.3) and for melanoma (SIR = 2.6 vs. 0.4). For breast cancer, the risks were nearly identical for the patients with pro-

gesterone deficiency and the patients with other causes of infertility. More of the resident patients than the referral patients were noted to have progesterone deficiencies (37 per cent vs. 25 per cent); this, for the most part, explained the previously observed differences in cancer risks by referral status, although resident patients continued to experience higher standardized incidence ratios than referral patients for breast cancer (SIR = 1.1 vs. 0.4 for patients with progesterone deficiencies and 1.1 vs. 0.7 for those with other causes of infertility).

A comparison of the medical record information for women with progesterone deficiencies with that for women with other causes of infertility showed no significant differences with respect to race, number of marriages, height, weight, number of pregnancies, previous dilation and curettage, gynecologic operations, and smoking or alcohol consumption. However, women with progesterone deficiencies more often had later ages at menarche, menstrual irregularity, histories of thyroid disease, and prior use of exogenous hormones; conversely, women with other causes of infertility had more recorded instances of pelvic inflammatory disease, venereal disease, and endometriosis.

The patients with other causes of infer-

TABLE 3

Observed and expected numbers of cancers and standardized incidence ratios (SIR) by cause of infertility (progesterone deficiency vs. other) among women evaluated for infertility at the Mayo Clinic, 1935–1964

| | Progesterone deficiencies (WY* = 15,964) | | | Other causes (WY = 29,444) | | |
|-------------|---|----------|-------|-------------------------------|----------|------|
| | Observed | Expected | SIR | Observed | Expected | SIR |
| All cancers | 62 | 54.13 | 1.15 | 86 | 92.64 | 0.93 |
| Colorectal | 5 | 6.67 | 0.75 | 12 | 10.12 | 1.19 |
| Lung | 8 | 3.50 | 2.28 | 4 | 3.11 | 0.65 |
| Melanoma | 3 | 1.16 | 2.58 | 1 | 2.33 | 0.43 |
| Breast | 17 | 18.57 | 0.92 | 32 | 33.39 | 0.96 |
| Cervix | 4 | 3.16 | 1.27 | 4 | 5.45 | 0.73 |
| Endometrium | 5 | 4.75 | 1.05 | 6 | 8.00 | 0.75 |
| Ovary | 5 | 3.15 | 1.59 | 6 | 5.46 | 1.10 |
| Thyroid | 4 | 0.77 | 5.20† | 2 | 1.54 | 1.30 |

* WY, women-years of follow-up.

† 95 per cent confidence interval 1.4–13.3.

tility were further divided into four groups (table 4), in the following order of priority, for the multiple recorded conditions: pituitary or metabolic disorders ($n = 391$), structural defects ($n = 436$), male factors ($n = 325$), and other or unknown problems ($n = 455$). Patients with pituitary or metabolic disorders or a male factor problem had lower expected overall cancer risks (SIR = 0.7 for both groups). An exception to this was a nonsignificantly elevated risk for colorectal cancer among patients with pituitary or metabolic disorders (SIR = 1.8). Subjects with structural defects demonstrated a standardized incidence ratio of 1.1 for all cancers, with a nonsignificant excess seen for cancer of the endometrium (SIR = 1.7). The study subjects who had other or unknown causes of infertility showed no unusually elevated cancer risks.

Selected cancer risks were also examined according to a number of other infertility parameters, including age at first evaluation, type of infertility (primary vs. secondary), and years of attempted conception. In general, these parameters were not predictive of cancer risk. However, patients evaluated prior to the age of 30 years experienced higher risks of colorectal (SIR = 1.4 vs. 0.7), lung (SIR = 1.7 vs. 0.7), and ovarian (SIR = 1.6 vs. 0.9) cancers, and a lower

risk of endometrial cancer (SIR = 0.7 vs. 1.0), than patients evaluated at older ages. Patients with primary infertility experienced a higher risk of breast cancer than those with secondary infertility (SIR = 1.0 vs. 0.6), while the opposite trend was seen for ovarian cancer (SIR = 1.2 vs. 1.9). Patients with short periods of attempted conception (less than five years) showed enhanced risks for cancers of the lung (SIR = 1.4 vs. 0.7) and breast (SIR = 1.0 vs. 0.6). Further analysis of special subgroups (e.g., women who were evaluated at young ages and who had extended periods of attempted conception) failed to show any further distinctive patterns of risk.

Analysis by age-specific years of follow-up showed that among the younger subjects (those less than age 50 years), there were nonsignificant increases in the risks of colorectal (SIR = 1.7) and endometrial (SIR = 1.7) cancers. There was no difference in risk for younger onset versus older onset breast cancer.

Cancer risks by years since first infertility evaluation are presented in table 5. There was no apparent relation of lung or breast cancers to increasing time since first evaluation. Endometrial cancer risk, which was elevated threefold in the first 10 years after infertility evaluation, showed a strik-

TABLE 4
Standardized incidence ratios by specific other causes of infertility among women evaluated for infertility at the Mayo Clinic, 1935-1964

| | Other causes of infertility | | | |
|-------------|---|------------------------------------|------------------------------|----------------------------------|
| | Pituitary or metabolic disorders (WY* = 7,568) | Structural defects (WY = 7,733) | Male factors (WY = 6,132) | Other or unknown (WY = 8,010) |
| All cancers | 0.69 (17)† | 1.14 (30) | 0.69 (12) | 1.11 (27) |
| Colorectal | 1.83 (5) | 1.00 (3) | 0.00‡ (0) | 1.51 (4) |
| Lung | 0.00‡ (0) | 1.72 (1) | 0.87 (1) | 1.28 (2) |
| Breast | 0.79 (7) | 0.97 (9) | 0.78 (5) | 1.25 (11) |
| Endometrium | 0.46 (1) | 1.73 (4) | 0.68 (1) | 0.00§ (0) |
| Ovary | 0.00 (0) | 1.29 (2) | 1.95 (2) | 1.40 (2) |

* WY, women-years of follow-up.

† No. of cases is shown in parenthesis.

‡ Expectation between 1.5 and 1.99.

§ Expectation between 2.0 and 2.49.

|| Expectation between 1.0 and 1.49.

TABLE 5
Standardized incidence ratios by years since first infertility evaluation, Mayo Clinic, 1935-1964

| | Years since first infertility evaluation | | | |
|-------------|--|-----------|-----------|-----------|
| | <10 | 10-19 | 20-29 | ≥30 |
| All cancers | 1.07 (19)* | 1.09 (49) | 1.07 (52) | 0.99 (28) |
| Colorectal | 1.59 (2) | 1.28 (5) | 1.49 (10) | 0.00† (0) |
| Lung | 2.86 (1) | 1.38 (3) | 0.68 (3) | 1.86 (5) |
| Breast | 0.94 (6) | 1.08 (20) | 0.78 (15) | 1.03 (8) |
| Endometrium | 3.41 (3) | 1.44 (5) | 0.35 (2) | 0.38 (1) |
| Ovary | 0.82 (1) | 1.04 (3) | 0.99 (3) | 3.25 (4) |

* No. of cases is shown in parenthesis.

† Expectation between 4.5 and 4.99.

ing decrease over time, with a deficit noted after 20 years of follow-up. The risk for ovarian cancer was highest after 30 years of follow-up (SIR = 3.2), but no trends in risk were seen prior to this time. When time trends were examined separately for the progesterone deficiency group, the same general patterns observed in the overall group were seen for cancers of the lung and breast. Endometrial cancer showed a decline with time, but the elevation in risk during the earliest time period was nonsignificantly elevated (SIR = 7.7). Trends for other sites were difficult to interpret because of small numbers.

Further analyses considered the effect of treatment on subsequent cancer risk. A total of 530 subjects (22.7 per cent) were given infertility medications, primarily estrogens or progestogens. Although the standardized incidence ratios were identical between treated and untreated subjects for all cancers and for breast cancer, there was some indication of higher risks among treated subjects for cancers of the lung (SIR = 1.8 vs. 1.1) and thyroid (SIR = 4.9 vs. 1.8). There was no difference in risk between treated and untreated subjects for endometrial cancer, although patients exposed to steroidal estrogens experienced a nonsignificant risk of 1.7.

Analysis of cancer risk by exposure information obtained for subjects through the end of follow-up revealed several interesting relations (table 6). Although there was no major difference in the overall cancer

risk by menopausal status, premenopausal onset accounted for all of the excess for cancers of the colon/rectum and lung. Breast cancer risk was similar for premenopausal and postmenopausal women. Examination of cancer risk by number of births showed decreased risk associated with multiple births for cancers of the breast and endometrium. Although breast cancer risk did not vary by age at first birth, there was some indication of a higher risk of cancer of the ovary with earlier ages at first birth (less than age 30 years) compared with later ages at first birth.

To evaluate the appropriateness of using Connecticut cancer incidence rates to derive expected values, we used the incidence rates of patients with other causes of infertility in selected analyses to derive expected values for those with hormonal causes of infertility. This slightly decreased the difference between the patients with progesterone deficiencies and those with other causes of infertility for cancers of the lung (SIR = 3.0) and cervix (SIR = 1.4), but it enhanced the effect for cancers of the endometrium (SIR = 1.6), ovary (SIR = 1.8), and thyroid (SIR = 4.5) and for melanoma (SIR = 9.1).

DISCUSSION

The results of this follow-up study are generally reassuring in terms of the cancer risk experienced by a cohort of women evaluated for infertility. The risk of all cancers was nearly identical to that expected, even

TABLE 6
Standardized incidence ratios by selected risk factors among women evaluated for infertility at the Mayo Clinic, 1935-1964

| | Menopausal status | | No. of births | | | Age (years) at first birth | |
|-------------|---------------------------------|---------------------------------|--------------------|---------------------|--------------------|----------------------------|---------------------|
| | Premenopausal (WY* = 27,485) | Postmenopausal (WY = 13,313) | 0 (WY = 25,138) | 1-2 (WY = 9,568) | ≥3 (WY = 6,992) | <30 (WY = 8,369) | ≥30 (WY = 8,191) |
| | | | | | | | |
| All cancers | 1.15 (61)† | 0.98 (76) | 1.08 (92) | 1.14 (37) | 0.45 (9) | 0.86 (17) | 0.89 (29) |
| Colorectal | 2.24‡ (10) | 0.67 (7) | 1.08 (11) | 0.57 (2) | 0.98 (2) | 1.13 (2) | 0.53 (2) |
| Lung | 2.51 (6) | 0.98 (6) | 1.25 (7) | 1.82 (4) | 0.00§ (0) | 0.78 (1) | 1.32 (3) |
| Breast | 1.01 (21) | 0.94 (24) | 0.95 (28) | 1.19 (14) | 0.54 (4) | 0.93 (7) | 0.94 (11) |
| Endometrium | 0.81 (3) | 0.92 (7) | 1.06 (8) | 0.71 (2) | 0.00 (0) | 0.00 (0) | 0.68 (2) |
| Ovary | 0.87 (3) | 1.47 (6) | 1.20 (6) | 2.65 (5) | 0.00§ (0) | 2.58 (3) | 1.05 (2) |

* WY, women-years of follow-up.

† No. of cases is shown in parenthesis. Unknowns are excluded from the analysis.

‡ 95 per cent confidence interval 1.1-4.1.

§ Expectation between 1.0 and 1.49.

|| Expectation between 1.5 and 1.99.

when the subjects were divided into those with progesterone deficiency versus those with other causes of infertility or when other attributes of the infertility were considered, such as age at first evaluation, primary versus secondary infertility, years of attempted conception, or years since first evaluation.

Since it has been proposed that the relations of nulliparity and age at first birth to breast cancer risk may result from some underlying hormonal abnormality, such as inadequate progesterone production, we examined the risk of breast cancer according to the various reasons for the infertility. In contrast to two previous studies that found excess risks of breast cancer among women with hormonal reasons for infertility (17, 18), we found no elevated risk of breast cancer (SIR = 0.9). In addition, breast cancer risk was not elevated when we considered other attributes of the infertility (e.g., primary vs. secondary infertility) or when we examined various ages at follow-up. Furthermore, the risk of breast cancer remained constant over follow-up time and was not altered when internal incidence rates were used to derive the expected number of cases.

Reasons for this discrepancy are not clear. In the study by Cowan et al. (17), the only elevation of breast cancer among the progesterone-deficient groups was for disease of premenopausal onset, based on nine observed cases, while there was actually a deficit postmenopausally. Ron et al. (18), however, found a 40 per cent excess of breast cancer at all ages, which reached a nonsignificant relative risk of 1.8 when women were further classified into those having adequate estrogen accompanied by deficient progesterone production. Since the latter study included women evaluated between 1964 and 1974, a period that post-dated accrual of patients in our study, their methods of classifying patients according to type of infertility were undoubtedly more precise than ours. This is supported by the fact that a substantially greater proportion of patients in that study had hormonal

causes of infertility (56 per cent vs. 31 per cent in our study), although to some extent this may reflect selection bias due to the reputation of the Chaim Sheba Medical Center for treating such disorders (E. Ron, National Cancer Institute, personal communication, 1988). However, despite the limitation in exposure classification, our study had certain strengths in terms of size and follow-up. In our study, we had 80 per cent power to detect a relative risk of 1.9 for breast cancer among patients with progesterone deficiencies. Thus, differences in results could relate to the greater precision of risk estimates in our study.

Given that nulliparous women experience increased risks of both endometrial and ovarian cancer, we expected to find some overall elevation of these rates. However, as with breast cancer, no significant excesses were observed for either endometrial or ovarian cancers (SIR = 0.9 and 1.3, respectively). However, the risks of both endometrial and ovarian cancer among women with progesterone deficiencies were at least 40 per cent higher than risks for women with other causes of infertility. The difference in risk between those with progesterone deficiencies and those with other causes of infertility was enhanced for both cancers when we used internal incidence rates to derive expected values, reflecting the fact that women in our cohort were unusual with respect to their eventual hysterectomy status. However, for endometrial cancer, apart from the earliest time period after evaluation, our risks were considerably lower than those reported by Ron et al. (18), who found an eightfold excess (95 per cent CI 2.5–19.3) among women with hormonal infertility on the basis of four observed events. A follow-up study of 1,270 women with chronic anovulation syndrome at the Mayo Clinic (20) showed a threefold increased risk of endometrial cancer. Although some of these same women may have been included in the present study (if they also sought advice for infertility after attempting to conceive for at least one

year), only 114 patients were classified as having luteal phase defects or polycystic ovary syndrome, of whom only one developed endometrial cancer (SIR = 1.9).

More provocative were the elevated risk estimates among women with progesterone deficiencies that we observed for melanoma (SIR = 2.6) and cancers of the thyroid (SIR = 5.2) and lung (SIR = 2.3). Although Ron et al. (18) also found an excess of melanoma and thyroid cancer, only their melanoma excess was associated with hormonal causes of infertility. Previous studies have indicated that either a late age at first birth (21) or nulliparity (22) increases the risk of melanoma, but not all studies have confirmed this (23, 24). A role for hormonal factors in the etiology of melanoma has been further suggested by associations with exogenous hormones (21, 24, 25) and by evidence of estrogen receptors in these tumors (26, 27). Thyroid cancer, on the other hand, has been found in several studies to relate directly to number of pregnancies (28–30), presumably because of enhanced production of thyroid-stimulating hormone during pregnancy. Further research is needed to clarify hormonal mechanisms in the carcinogenesis of both thyroid cancers and melanoma.

The lung cancer excess seen among our patients with progesterone deficiencies was unexpected. Of concern was the possibility of confounding by smoking status, since the risk of lung cancer was reduced somewhat when internal incidence rates were used. Analysis of smoking information (available for 87 per cent of the total population) revealed that seven of the eight observed lung cancer cases occurred among smokers. However, among smokers, lung cancer was elevated only for those with hormonal causes of infertility (SIR = 6.3) and not for those with other causes of infertility (SIR = 0.9). The possibility that smoking alters susceptibility to hormonal factors through immunologic or other mechanisms deserves further attention, particularly given observations that smokers often have reproduc-

tive difficulties (31, 32), early ages at natural menopause (33, 34), and low levels of urinary estrogens (35).

In interpreting the results of this study, several methodological issues are of concern. Foremost was our limited success in tracing these women so many years after their infertility evaluations. Although our overall follow-up rate (67 per cent) was nearly identical to that achieved by Cowan et al. (17) on patients from the same era, our losses were considerably greater than those experienced by Ron et al. (18), where 96 per cent of women treated for infertility between 1964 and 1974 were successfully matched against the Israeli Cancer Registry. We did note some baseline differences between patients who were traced and those lost to follow-up; most bothersome was the fact that lost patients more often were smokers and had histories of pelvic infections, which was of particular concern in terms of an underestimation of cancers of the lung and cervix. Some support for this derives from the fact that standardized incidence ratios for both of these cancers were somewhat higher for the Olmsted County residents. However, it is reassuring that there were few other differences in risk factors between the traced and the lost patients, particularly with respect to factors that would affect the cancers of primary interest, for example, cancers of the breast, endometrium, and ovary.

Of further concern was the appropriateness of the incidence rates used to derive expected numbers of cancer cases. Although Connecticut cancer incidence rates have been shown to correspond to rates for Olmsted County (36), there is no obvious standard for referral patients. Of greater concern was the appropriateness of comparing this rather unusual cohort of women with the general population. However, when internal incidence rates were used to examine risks among specific subgroups (e.g., hormonal vs. nonhormonal), the same basic conclusions were reached, with the exception that the endometrial cancer ex-

cess among the hormonal group was somewhat enhanced.

Finally, the possibility of exposure misclassification must be addressed. The means of distinguishing hormonal causes from other causes of infertility were crude at the time of evaluation. Even though analyses were based on a crude classification, the higher risks of certain other cancers among women with progesterone deficiencies are of interest. The higher risk of endometrial cancer supports the well established role of unopposed estrogens in the etiology of the disease, while the ovarian cancer excess implies, as first proposed by Joly et al. (10), that an underlying endocrine abnormality may be more important than a protective effect of pregnancy on risk. Although the cancer sites observed were not hypothesized a priori as sites that would specifically relate to hormonal causes of infertility, and although the relations were possibly due only to chance, the elevations of risk observed for thyroid and lung cancers and melanoma are of interest and warrant further evaluation using more precise exposure classification.

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