Intrauterine device use and risk of endometrial cancer

F. Parazzini1,2, C. La Vecchia1,2 & S. Moroni1,2
1Istituto di Ricerche Farmacologiche ‘Mario Negri’, Milan, Italy: 2Clinica Ostetrico Ginecologica, Università di Milano, Milan, Italy: 1Istituto di Biometria e Statistica Medica, Università di Milano, Milan, Italy.

Summary The relationship between intrauterine device (IUD) use and risk of endometrial cancer has been analysed in a case-control study conducted in Italy between 1983 and 1992, including 453 patients with histologically confirmed endometrial cancer and 1,451 controls admitted for acute, non-gynaecological, non-hormonal, non-neoplastic conditions to the same network of hospitals where cases had been identified. Two (0.4%) cases versus 36 (2.3%) controls reported ever using an IUD. The corresponding multivariate relative risk was 0.4 (95% CI 0.1–1.0). The results of this study and the few published available epidemiological data suggest a protective role of IUD use on endometrial carcinogenesis, but potential selective mechanisms for IUD utilisation (indication bias) should be carefully considered in the interpretation.

Intrauterine device (IUD) use may induce endometrial alterations, such as inflammatory changes (Sheppard, 1987), loss of epithelial surface (El-Badrawi et al., 1981) and reduction in ciliated cells (Gonzalez-Angulo et al., 1973), which may affect the risk of neoplastic changes of the endometrium. In terms of biological inference, the risk of endometrial cancer might be either increased or decreased by such changes.

Epidemiological data on the relation between IUD use and risk of endometrial cancer are, however, scanty. A recent analysis of data from the Cancer and Steroid Hormones (CASH) Study suggested that the risk of endometrial cancer is approximately halved in women reporting ever IUD use, and the protective effect tended to increase with duration of use (Castellsague et al., 1993). To offer further data on the issue, we report the results from a case-control study conducted in Northern Italy (Parazzini et al., 1991a).

Patients and methods

The general design of this study has been previously described (Parazzini et al., 1991a). Cases included in the study were 453 patients with histologically confirmed endometrial cancer aged <65 years (median age 56 years, range 28–64). They were admitted to the Ospedale Maggiore (including the four largest teaching and general hospitals in the greater Milan area), to the University Obstetrics and Gynecology Clinics and to the National Cancer Institute of Milan between 1983 and 1992. They were interviewed during their stay in hospital for surgery, medical treatment, radiotherapy: their diagnosis of endometrial cancer dated back no more than the 1 year (median time from diagnosis to interview 2 months, range 0–12 months).

Controls were patients younger than 65 years admitted for acute, non-gynaecological, non-hormone-related, non-neoplastic conditions to the same network of hospitals where cases had been identified. Women who had undergone hysterectomy were not eligible as controls. A total of 1,541 controls (median age 53 years, range 27–64) was included in the present analyses. Of these, 32% were admitted for traumatic conditions (mostly fractures and sprains), 35% had non-traumatic orthopaedic disorders (mostly low back pain and disc disorders), 15% had surgical conditions (mostly abdominal, such as acute appendicitis or strangulated hernia) and 18% had other illnesses, such as ear, nose and throat or dental disorders. Less than 3% of identified cases and controls refused to be interviewed.

Trained interviewers identified and questioned cases and controls using a standard questionnaire. Information was collected on general characteristics and habits, gynaecological and obstetric data, related medical history and use of oral contraceptives, intrauterine devices (IUD) and female hormones for other indications.

Odds ratios, as estimators of relative risks (RR) of endometrial cancer, together with their 95% confidence intervals (CI), according to use of IUD were computed from data stratified for quinquennia of age by the Mantel–Haenszel procedure (Mantel & Haenszel, 1959). In order to allow simultaneously for the effects of several potential confounding factors, unconditional multiple logistic regression, with maximum likelihood fitting, was used (Breslow & Day, 1980). Included in the regression equations were terms for age and selected factors significantly associated in this data set with the risk of endometrial cancer (parity, Quetelet’s index and oestrogen replacement therapy use).

Results

The distribution of cases and controls according to age and selected covariates is presented in Table I. Cases were more frequently nulliparous (RR age adjusted, parae versus nulliparous, 0.6; 95% CI 0.4–0.9), of higher body mass index (age adjusted RR, kg m⁻² ≥ 25 vs <25, 2.0; 95% CI 1.7–2.4) and more often oestrogen replacement therapy users (RR ever versus never 2.0, 95% CI 1.3–3.1).

The relation between IUD use and endometrial cancer risk is considered in Table II. Out of the 453 endometrial cancer cases, two (0.4%) reported ever having used an IUD: the figures for controls were 36 ever users (2.3%) out of the 1,541 controls. The corresponding RR of endometrial cancer was, in comparison with never users, 0.4 (95% CI 0.1–1.0) for ever IUD users. The data were insufficient for analysis of duration of use or other time-related factors.

Discussion

The results of this analysis further suggest that IUD use reduces the risk of endometrial cancer, but the interpretation deserves caution. In fact, indication bias may, at least partially, explain this inverse association. IUD may be less frequently prescribed in women with long, heavy menstrual flows or reporting pre-, post- or inter-menstrual blood spotting, conditions that may be associated with unopposed oestrogen endometrial stimulation and consequently increased endometrial cancer risk. Another potential limitation of this study is the low number of IUD users in Italy, which did not provide the opportunity to analyse the role of duration and any other time-related factors. In relation to other potential

Correspondence: F. Parazzini, Istituto di Ricerche Farmacologiche ‘Mario Negri’, via Eritrea, 62-20157 Milan, Italy.
Received 17 December 1993; and in revised form 31 March 1994.

Br. J. Cancer (1994). 70, 672–673 © Macmillan Press Ltd., 1994
Table 1 Distribution of 453 endometrial cancer cases and 1,541 controls according to selected characteristics, Milan, Italy, 1983–1992

| Cases | Controls |
|-------|----------|
| Age (years) | | |
| <0.45 | 37 (8.2) | 188 (12.2) |
| 0.45–0.54 | 145 (32.0) | 690 (44.8) |
| >0.54 | 271 (59.8) | 663 (43.0) |
| Education (years) | | |
| <0.7 | 300 (66.2) | 925 (60.0) |
| 0.7–1.1 | 94 (20.8) | 372 (24.1) |
| >1.2 | 59 (13.0) | 244 (15.8) |
| No. of births | | |
| 0 | 101 (22.3) | 273 (17.7) |
| 1–2 | 244 (53.9) | 875 (56.8) |
| >3 | 108 (23.8) | 393 (25.5) |
| Quetelet’s index (kg m⁻²) | | |
| <25 | 197 (43.5) | 898 (58.3) |
| 25–30 | 147 (32.5) | 478 (31.0) |
| >30 | 109 (24.1) | 165 (10.7) |
| Oral contraceptive use | | |
| Never | 431 (95.1) | 1436 (93.2) |
| Ever | 22 (4.9) | 105 (6.8) |
| Oestrogen replacement therapy | | |
| Never | 408 (90.1) | 1468 (95.3) |
| Ever | 45 (9.9) | 73 (4.7) |

Table 2 Distribution of 453 endometrial cancer cases and 1,541 controls according to indicators of IUD use, Milan, Italy 1983–1992

| IUD use | Endometrial cancer | Controls |
|---------|---------------------|---------|
| | Relative risk (95% confidence interval) |
| Never | 451 | 1505 |
| Ever | 2 | 36 |

References

BRESLOW, N.E. & DAY, N.E. (1980). Statistical Methods in Cancer Research. Vol. 1. The Analysis of Case–control Studies. IARC Scientific Publication No. 32. IARC: Lyon.

CASTELLAGUE, X., THOMPSON, W.D. & DUBROW, R. (1993). Intrauterine contraception and the risk of endometrial cancer. Int. J. Cancer. 54, 911–916.

EL-BADRAWI, H.H., HAFEEZ, E.S.E., BARNHART, M.I., FAYAD, M. & SHAFFEK, A. (1981). Ultrastructural changes in the human endometrium with copper and non-mediated IUDs in uterus. Fertil. Steril. 36, 41–49.

GONZALEZ-ANGULO, A., AZNAR-RAMOS, R. & FERIA-VELASCO, A. (1973). Ultrastructural changes found in endometrium of women using Lippes intrauterine device. J. Reprod. Med., 10, 44–51.

MANTEL, N. & HAENSZEL, W. (1959). Statistical aspects of data from retrospective studies of disease. J. Natl Cancer Inst., 22, 719–748.

MYATT, L., ELDER, M.G. & LIM, L. (1980). Alterations in progesterone receptors in the rat uterus bearing an intra-uterine device during the oestrous cycle and early pregnancy. J. Endocrinol., 77, 365–373.

PARAZZINI, F., LA VECCHIA, C., NEGRE, E., FEDDE, L. & BALOTTA, F. (1991a). Reproductive factors and risk of endometrial cancer. Am. J. Obstet. Gynecol., 164, 522–527.

PARAZZINI, F., LA VECCHIA, C., BOCCIOLONE, L. & FRANCESCHI, S. (1991b). The epidemiology of endometrial cancer. Gynecol. Oncol., 41, 1–16.

SHEPPARD, B.L. (1987). Endometrial morphological changes in IUD users: a review. Contraception, 36, 1–10.

TAMAYA, T., NAKATA, Y., OHNO, Y., NIKA, S., FURUTA, N. & OKADA, H. (1976). The mechanism of action of the copper intra-uterine device. Fertil. Steril., 27, 767–772.

This work was conducted within the framework of the CNR (Italian National Research Council) applied projects Clinical Applications of Oncological Research (Contract No. 92.02384 PF39) and Prevention and Control of Disease Factors (Contract No. 92.00229 PF41) and with a grant in aid from the Europe Against Cancer Program of the Commission of the European Community. The generous contributions of the Italian Association for Cancer Research, of the Italian League against Tumors, Milan, Italy, and of Mrs Angela Marchegiano Borgomaniero are gratefully acknowledged. Ms Judy Bagott, Ivana Garimboldi and the G.A. Pfeiffer Memorial Library Staff provided helpful editorial assistance.