International Journal of Epidemiology
© International Epidemiological Association 1992

Vol. 21, No. 5
Printed in Great Britain

Letters to the Editor

Use of Intrauterine Device and Risk of Invasive Cervical Cancer

From FABIO PARAZZINI,*,† CARLO LA VECCHIA*,‡ AND EVA NEGRI*

Sir—We have read with interest the paper of Lassise *et al.* recently published by the IJE on the relation between use of intrauterine devices (IUD) and risk of invasive cervical cancer.[1] That study, conducted in five metropolitan areas in the US on 481 cases and 801 general population controls, showed a nonsignificant reduced risk of invasive cervical cancer associated with copper IUD use (relative risk [RR] 0.6, 95% confidence interval [CI] : 0.3–1.2), but not with inert IUD use (RR 1.1, 95% CI : 0.9–1.7). To offer further data on this issue we would like to add the following.

The study by Lassise *et al.* is well conducted; however, there is considerable uncertainty about the relation between IUD use and risk of invasive and intraepithelial cervical cancer, with other reports showing an increased risk of cervical cancer in ever IUD users.[2–4] We have analysed data collected in a case-control study conducted in North Italy,[5] an area characterized by a low prevalence of IUD use. A total of 720 histologically confirmed invasive cervical cancer cases (median age 52, range 22–74) and 820 controls (median age 54, range 20–74) in hospital for acute, non-hormonal or gynaecological conditions (27% traumas, 33% non-traumatic orthopaedic disorders, 15% acute surgical conditions and 25% other miscellaneous conditions) were interviewed.

RR estimates and the corresponding 95% CI of invasive cancer in relation to IUD use were computed using multiple logistic regression. Included in the regression were terms for age, education, parity, smoking, age at first intercourse, lifetime number of sexual partners, contraceptive use, number of Pap smears and years since last Pap smear.

The main results are shown in Table 1. A total of 20 (2.8%) cases and 38 (4.6%) controls had ever used an IUD, for a crude RR of 0.6 (95% CI : 0.3–1.0). There was no evidence of a duration-risk relationship, the crude RR estimates being 0.6 in women reporting a use lasting 3 years or less and 0.7 for more than 3 years. Likewise no relation emerged with time since last use.

TABLE 1 *Distribution of 720 cervical cancer cases and 820 controls, and corresponding relative risk, according to IUD use (Milan, Italy)*

	Cervical cancer	Controls	RR (95% CI)[a]	
			Crude	MLV[b]
IUD use				
No	700[c]	782	1[d]	1[d]
Yes	20	38	0.6 (0.3–1.0)	0.6 (0.3–1.1)
Duration of use (years)				
≤3	9	18	0.6 (0.3–1.2)	0.5 (0.2–1.3)
>3	11	18	0.7 (0.3–1.4)	0.6 (0.3–1.5)
Time since last use (years)				
<5	11	24	0.5 (0.3–1.0)	0.6 (0.2–1.4)
≥5	8	9	1.0 (0.4–2.6)	0.7 (0.3–1.6)

[a] RR = relative risk. CI = confidence interval.
[b] Multivariate estimates adjusted for age, education, parity, smoking, age at first intercourse, number of sexual partners, oral contraceptive use, number of Pap smears and years since last Pap smear.
[c] In some cases the sum does not add up to the total because of missing values.
[d] Reference category.

These results offer some support to the suggestion that IUD use may reduce the risk of invasive cervical cancer and are, therefore, at least in part supportive of the paper by Lassise *et al.*[1] The estimated RR was however of borderline statistical significance (possibly for the small number of users) and no trend in risk was found with duration of use.

The protective effect of IUD use has been discussed by Lassise *et al.*[1] on the basis of an effect of copper in decreasing enzyme production and synthesis of DNA and carbohydrate, mucopolysaccharide metabolism. However, we were not able in our study to analyse separately the effects of copper or inert IUD. It is possible that stronger protection exists from copper IUD use. In any case these results do not support a direct relationship between invasive cervical cancer and IUD use.

* Istituto di Ricerche Farmacologiche 'Mario Negri', via Eritrea 62, 20157 Milan, Italy.
† II Clinica Ostetrico Ginecologica, University of Milan, 20100 Milan, Italy.
‡ Institute of Social Preventive Medicine, University of Lausanne 1005, Lausanne, Switzerland.

ACKNOWLEDGEMENTS

This work was conducted within the framework of the CNR (Italian National Research Council) Applied Project 'Oncology' (Contract 87.01544.44) and 'Prevention and Control of Disease Factors' (Contract 91.00285. PGF1), and with the contributions of the Italian Association for Cancer Research and the Italian League Against Tumours, Milan, Italy.

REFERENCES

[1] Lassise D L, Savitz D A, Hamman R F *et al.* Invasive cervical cancer and intrauterine device use. *Int J Epidemiol* 1991; **20**: 865–70.

[2] Pincus G, Garcia C R. Studies on vaginal, cervical and uterine histology. *Metabolism* 1965; **14**: 344–47.

[3] Jones M C, Buschmann B O, Dowling E A. The prevalence of actinomycetes-like organisms found in cervico-vaginal smears of 300 IUD wearers. *Acta Cytol* 1979; **23**: 282–86.

[4] Engineer A D, Misra J S, Tandon P. Long-term cytologic studies of copper-IUD users. *Acta Cytol* 1981; **25**: 550–56.

[5] Parazzini F, La Vecchia C, Negri E *et al.* Oral contraceptive use and invasive cervical cancer. *Int J Epidemiol* 1990; **19**: 259–63.

Effects of Environment and Passive Smoking on the Respiratory Health of Children

From C M WONG AND D J SPIEGELHALTER

Sir—We refer to an article by Francesco Forastiére *et al.*[1]

In the study described in the article, two polluted areas were chosen and were compared with a control area in order to evaluate the effects of air pollution on the respiratory health of schoolchildren. Seventeen schools in the areas were randomly selected and all the 3092 children in the required grades were recruited. In the data analyses, logistic regressions were used to obtain the odds ratios for the two polluted areas and for parental smoking, with adjustments for various potential confounding factors. However, no account was taken of the between subject correlation produced as a result of sampling from the schools instead of from the individual subjects.

A basic requirement for a valid logistic regression analysis is the assumption of independence between individual observations. Unless adjustments are made by some means, the effect of ignoring the lack of independence will be underestimation of the standard error and hence a narrower confidence interval (CI) being used erroneously in the analysis. In Table 3 of the article, the odds ratios with 95% CI for the eight respiratory symptoms in the industrial area (Civitavecchia) and the urban area (Rome) were reported. In both areas, three symptoms were found to have 95% CI greater than one, but with lower limits all below 1.06. Had the correlation been taken into account, it is likely that these CI would not have excluded 1.00.

Biostatistics Unit, Medical Research Council, Institute of Public Health, University Forvie Site, Robinson Way, Cambridge CB2 2SR, UK.

Techniques for dealing with such dependence are becoming increasingly available. Williams' method of adjustment by means of an iterative reweighted procedure[2] is described in Collett[3] with provision of a GLIM macro. However this method only works on grouped data and on the assumption that the degree of correlation is uniform among the subunits of the sample. In practice, random effects modelling methods can be used to take account of the extra variation due to between subject correlation. Some computational procedures are available in the statistical package EGRET.[4] Multilevel modelling techniques[5] can also be used to explain the sources of the extra variation using the statistical package ML3.[6] Skinner *et al.*[7] contains a good discussion of the issues, and describes other approaches in analysing complex survey data.

REFERENCES

[1] Forastière F, Corbo G M, Michelozzi P *et al.* Effects of environment and passive smoking on the respiratory health of children. *Int J Epidemiol* 1992; **21**: 66–73.

[2] Williams D A. Extra-binomial variation in logistic linear models. *Applied Statistics* 1982; **31**: 144–48.

[3] Collett D. *Modelling Binary Data*. London: Chapman & Hall, 1st edn. 1991.

[4] *EGRET reference manual*. Statistics & Epidemiology Research Corp and Cytel Software Corp, 1985–89.

[5] Goldstein H. Multilevel mixed linear model analysis using iterative generalized least squares. *Biometrika* 1986; **73**: 43–56.

[6] Prosser R, Rasbash J and Goldstein H. ML3 software for three-level analysis users' guide for v.2. London: Institute of Education, University of London, 1991.

[7] Skinner C J, Holt D and Smith T M F (eds). *Analysis of Complex Surveys*. New York: John Wiley & Sons, 1989.