# PAPERS AND SHORT REPORTS



## Oral contraceptives and hepatocellular carcinoma

J NEUBERGER, D FORMAN, R DOLL, ROGER WILLIAMS

### Abstract

**A series of 26 white women aged under 50 who developed hepatocellular carcinoma in a non-cirrhotic liver were studied for the possible role of oral contraceptives. Eighteen of the women had used the "pill" for a median of eight years. Over 1300 women whose use of the pill had been determined in another study served as controls. Patients and controls were divided into five age and four calendar groups and the relative risks associated with oral contraceptives calculated by multivariate analysis.**

**Short term use of the pill was not associated with an increased risk of tumour development; nevertheless, use for eight years or more was associated with a 4·4-fold increased risk ($p<0·01$). When patients with markers of hepatitis B virus infection were excluded the relative risk was 7·2 ($p<0·01$). In both instances the absolute risk for developing hepatoma remained low.**

### Introduction

A causal relation between usage of oral contraceptives and benign hepatic adenomas is generally agreed,[1-4] but whether this also applies to hepatocellular carcinoma is more controversial. The increased incidence of adenoma since the introduction of the "pill,"[5,6] the relation with both its duration of use and its oestrogenic potency, and the statistically significant evidence from controlled case studies[7,8] have not been matched by equally convincing data for hepatocellular carcinoma. Anecdotal reports of women taking the pill developing hepatocellular carcinoma[9] do, however, include two cases in which malignant changes were found along with areas of adenoma formation,[10,11] and the results of two large tumour registry surveys were consistent with a possible association.[6,12] More recently, Henderson and colleagues from Los Angeles showed that women with hepatocellular carcinoma diagnosed between 1975 and 1980 had a greater use of the pill than matched controls,[13] and Forman *et al* in Britain found a small but consistent increase in mortality due to hepatocellular carcinoma among women during 1950-81,[14] which continued in 1982 and 1983. (In 1967-73 death certification rates per million women aged 20-39 and 40-54 years were 1·0 and 5·6 respectively; in 1982-3 these rates were 1·7 and 8·4—D Forman, unpublished results.) A similar trend in countries such as the United States and Australia, where use of the pill is comparable to that in Britain, was, however, not seen, and two recent reviews cast considerable doubt on the causality of the relation.[9,15]

We have reviewed our clinical experience of hepatocellular carcinoma in women under 50 with non-cirrhotic livers and taking the pill and estimated the relative risk of tumour development in pill users.

### Patients and methods

Twenty six white women aged under 50 and resident in Britain were admitted to the liver unit between the beginning of January 1976 and March 1985. In each instance a hepatocellular carcinoma in a non-cirrhotic liver was confirmed histologically. Eighteen women had taken oral contraceptives before presentation, including five described elsewhere.[16] Table I shows the age distribution of the women and their history of oral contraceptive usage. None had hepatitis B surface antigen in serum tested by radioimmunoassay, though one of the 18 pill users had serological evidence of past infection with hepatitis B virus (antisurface antibodies), as had three of the eight non-users (anticore antibodies). α Fetoprotein concentrations were raised more than 100 μg/l in three of the pill users and four of the non-users. The differences

TABLE I—*Distribution of cases of hepatocellular carcinoma by age and oral contraceptive usage*

| Age (years) | History of oral contraceptive usage | | | | |
|---|---|---|---|---|---|
| | Never | <4 Years | 4-7 Years | ≥8 Years | Ever |
| <30 | 3 | 3 | 3 | 1 | 7 |
| 30-4 | 1 | | | 2 | 2 |
| 35-9 | 1 | | 1 | 2 | 3 |
| 40-4 | 1 | 1 | 1 | 3 | 5 |
| 45-9 | 2 | | | 1 | 1 |
| All ages | 8 | 4 | 5 | 9 | 18 |

**The Liver Unit, King's College School of Medicine and Dentistry, London SE5 8RX**

J NEUBERGER, DM, MRCP, Wellcome senior clinical research fellow and honorary senior lecturer

ROGER WILLIAMS, MD, FRCP, director of liver unit

**Imperial Cancer Research Fund, Epidemiology Unit, Radcliffe Infirmary, Oxford**

D FORMAN, PHD, research fellow ICRF

R DOLL, FRS, honorary consultant, ICRF

Correspondence to: Dr Williams.

between pill users and non-pill users in both cases were of borderline significance (Fisher's exact test: p=0·07 and p=0·17 respectively). None of the women had a daily alcohol intake of more than 40 g.

The use of oral contraceptives by the patients with tumours was compared with that found in 1333 women as part of a case-control study of breast cancer in London and Oxford.[17,18] Patients and controls were divided into five age groups (<30, 30-34, 35-39, 40-44, and 45-49) and four calendar groups (1976-7, 1978-9, 1980-1, 1982-4) representing the date of diagnosis for the women with hepatocellular carcinoma and the date of interview of the controls.

Within each age and calendar group the expected number of cases for each different duration of pill use (<4, 4-7, ≥8 years) was calculated using the proportions found among the control women. The relative risk was calculated by multivariate analysis and summation over all the age and calendar groups. The analysis was also done after excluding all patients serologically positive for hepatitis B virus.

## Results

### CLINICAL FEATURES OF HEPATOCELLULAR CARCINOMA ASSOCIATED WITH THE PILL

Upper abdominal or right sided chest pain was the most common presenting symptom (10 patients). Four patients had noticed a painless mass in the right upper quadrant. Other presenting symptoms included weight loss (one patient), anaemia (one), night sweats (one), and obstructive jaundice (one). Hepatomegaly, usually massive, was present in all but two, and in one patient the spleen was also enlarged. Serum liver function values were abnormal in all but one patient, showing a pattern consistent with a space occupying lesion, with a median serum alkaline phosphatase activity of 560 IU/l (upper range of normal 85 IU/l) and γ-glutamyltransferase activity of 550 IU/l (upper limit of normal 45 IU/l). Serum bilirubin concentrations were only minimally raised with the exception of one patient with obstructive jaundice due to hilar duct obstruction by the mass.

Histological examination showed a well differentiated hepatocellular carcinoma in nine cases and a poorly differentiated tumour in five. There were two instances each of the fibrolamellar and clear cell variants. Radioisotope or ultrasound scan showed a unifocal lesion in all but three patients, who had multiple nodules of similar size throughout the liver.

In only three of the 18 patients was resection possible. One was alive and well seven years later, one died with extrahepatic metastases 18 months after resection, and the other developed recurrences in the remaining lobe 5·8 years later and was given an orthotopic liver transplant (Professor R Y Calne); unfortunately, this patient died within two months of grafting with widespread metastases. Three other patients had a liver transplantation carried out at the time of first presentation; two died four and 15 months later from disseminated metastases and the third was well at six months. The remaining 12 patients were treated by chemotherapy with prior hepatic artery embolisation or ligation in five; one was alive at 10 months and survival periods in the others ranged from one to 15 months (median six months).

### USE OF THE PILL AND RELATIVE RISK ASSESSMENT

Seven women had been taking preparations containing 30 μg of oestrogen or less and 10 had taken preparations containing 50 μg or more. One 29 year old woman with a history of neuroblastoma in childhood, radiation induced ovarian damage, and induction of the menarche by ethinyloestradiol and norethisterone had received maintenance treatment with contraceptive hormones for 12 years.

Table II shows the estimated relative risks for the development of hepatocellular carcinoma in users of oral contraceptives. Comparison of never users with ever users or users for up to eight years showed no increased relative risk; prolonged use of the pill, however, was associated with a 4·4-fold greater risk (p<0·01). When the four patients with serological evidence of past hepatitis B virus infection were excluded from the analysis the risk increased to 7·2 (p<0·01).

## Discussion

Although this series of women with hepatocellular carcinoma represents one of the largest reported from a single centre, the absolute number of cases is still small and the estimates of relative risk associated with use of oral contraceptives depend on several important assumptions. Firstly, we have assumed that the pattern of referral of women with hepatocellular carcinoma to our unit was unaffected by a history of oral contraception. We cannot prove that this was so, but nor do we have any reason to doubt it. Secondly, the liver unit received patients from the whole country, whereas all the controls were resident in the south of England. If there are regional variations in prescribing oral contraceptives this could affect the results. Nevertheless, of the 13 patients with hepatocellular carcinoma for whom a residential history was available, 10 lived in the south. Thirdly, the histories of oral contraception in the cases and controls were obtained and recorded by different interviewers using different questionnaires, though it is difficult to see how this could have distorted our results.

Given these caveats, our results suggest that the risk of hepatocellular carcinoma is increased by oral contraceptives, especially when these are used for eight years or more. The lower relative risk of hepatoma in women with less than four years' use is difficult to explain and is presumably a chance result, as it was not found in the series of Henderson *et al.*[13] The increase in relative risk of hepatocellular carcinoma associated with long term use of oral contraception in our study (4·4 for all cases, 7·2 for cases without evidence of hepatitis B infection), while substantial, is much less than that for adenoma. For that condition the relative risk after five years' use of oral contraceptives has been estimated to lie between 100 and 500.[7,8] Furthermore, the absolute risk of hepatocellular carcinoma associated with the pill remains very small because the disease is so rare. (Given an overall mortality of two deaths per million women aged 20-49 with roughly 14% having eight or more years' use of oral contraceptives, then a maximum of 12 cases of hepatocellular carcinoma a year would be attributable to long term pill usage in England and Wales.) Nevertheless, these findings would be consistent with results in laboratory animals which have shown that sex steroids may act as initiators or promoters of carcinogenesis.[19-23] It has also been suggested that the oestrogen contained in the pill acts by inducing vascular changes or by inducing cell hypertrophy[24] and that this results in earlier presentation of an already developing tumour.

There may, of course, be other factors in addition to the pill in the development of tumours in these women. Heavy smoking has recently been suggested.[25] In our patients for whom smoking histories were available no differences between pill users and non-users could be discerned. The possible role of hepatitis B infection is difficult to assess, for studies by Brechot and his colleagues have shown that hepatitis B virus deoxyribonucleic acid (DNA) can be found integrated into the host genome in a significant percentage of patients with hepatoma even in the absence of serum markers of infection.[26] M Bassendine (personal communication) has found integrated hepatitis B virus DNA in tumour tissue from one woman

TABLE II—*Relative risks of hepatocellular carcinoma in oral contraceptive users compared with non-users*

| Use | No of cases: Observed | No of cases: Expected* | Estimate of relative risk† (95% confidence intervals) |
|---|---|---|---|
| *Total group* | | | |
| Never user | 8 | 7·3 | 1·0 |
| Ever user | 18 | 18·7 | 1·0 (0·4-2·4) |
| <4 years | 4 | 11·4 | 0·3 (0·1-1·1) |
| 4-7 years | 5 | 5·0 | 0·9 (0·3-3·4) |
| ≥8 years | 9 | 2·3 | 4·4** (1·5-12·8) |
| *Total group excluding women with markers of hepatitis B virus* | | | |
| Never user | 5 | 5·9 | 1·0 |
| Ever user | 17 | 16·1 | 1·5 (0·5-4·4) |
| <4 years | 4 | 9·8 | 0·5 (0·1-1·9) |
| 4-7 years | 5 | 4·5 | 1·5 (0·4-6·3) |
| ≥8 years | 8 | 1·8 | 7·2** (2·0-25·7) |

* Expected numbers based on distribution of usage of oral contraceptives in control women. Women were divided into two calendar groups (1976-9 and 1980-4) and five age groups (<30, 30-34, 35-39, 40-44, and 45-49). Proportions of control women in different usage categories were then applied to patient series.

† Relative risk estimates calculated using logistic regression model after stratifying into four calendar periods (1976-7, 1978-9, 1980-1, 1982-4) and five age groups (<30, 30-34, 35-39, 40-44, and 45-49).

** p<0·01.

with a hepatoma who had been taking hormone replacement therapy and in whom serum markers were absent.

Though the chances of a woman taking the pill developing a hepatocellular carcinoma are low, the possibility needs to be considered in any woman with a long history of contraceptive use who develops new symptoms of right upper or central abdominal pain or in whom unexplained hepatomegaly is found. Further investigation by the non-invasive technique of ultrasound together with liver function tests should be enough to indicate the likelihood of a tumour of the liver.

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# Cancer of the liver and the use of oral contraceptives

D FORMAN, T J VINCENT, R DOLL


## Abstract

**A case-control study of the use of oral contraceptives was conducted among women certified as having died from cancer of the liver in the period 1979-82 and in the age range 20-44 years. An age matched group of women who died from other causes, not related to use of oral contraceptives, in the same period were used as controls. Information about use of oral contraceptives was obtained from the general practitioners' notes for both cases and controls. Information was obtained for 30 women with histologically confirmed liver cancer, 19 with hepatocellular carcinoma and 11 with cholangiocarcinoma, and for 147 controls. The results were analysed after adjusting for age at diagnosis and year of birth and showed that use of oral contraceptives was associated with a significantly ($p<0.05$) raised relative risk for hepatocellular carcinoma of 3·8 (95% confidence interval 1·0 to 14·6) and use for eight years or more was associated with a significantly ($p<0.01$) increased relative risk of 20·1 (2·3 to 175·7). There were no apparent increases in risk for cholangiocarcinoma. Despite the small number of cases in this study and the methodological problems in assessing use of oral contraceptives from general practitioners' notes, the results were consistent with other similar studies. Although in the United Kingdom primary liver cancer remains an exceptionally rare disease, especially in young women, further research on the role of oral contraceptives is needed in those countries where it is a much more common disease.**


**Imperial Cancer Research Fund, Cancer Epidemiology and Clinical Trials Unit, Gibson Building, Radcliffe Infirmary, Oxford**

D FORMAN, PHD, research fellow
T J VINCENT, BSC, research officer
R DOLL, FRS, FRCP, FFCM, honorary consultant

Correspondence to: Dr Forman.

## Introduction

The evidence that oral contraceptives may cause primary hepatocellular carcinoma in women rests almost entirely on anecdote or evidence from uncontrolled studies. Nevertheless, the number of cases of malignant liver tumours in young women taking oral contraceptives, based on individual reports,[1] and more systematic surveys,[2-4] continues to rise. Over 100 such cases have now been reported, and in England and Wales national mortality rates show a slight increase for this rare disease in women under the age of 50 since the mid-1960s when the use of oral contraceptives became widespread.[5] Several abnormal characteristics associated with the pathology and natural history of hepatocellular carcinoma in young users of oral contraceptives have also been noted. The tumours usually occur in non-cirrhotic livers,[3] without associated hepatic fibrosis[3] or raised α fetoprotein concentrations.[3,6] This evidence, together with the occasional reports of malignancy progressing from benign adenoma,[7,8] which is certainly associated with the use of oral contraceptives,[9] suggests that there could be a specific group of liver carcinomas related to oral contraceptives.

To date there has been only one published case-control study specifically designed to investigate this question,[10] and this was