

BRIEF COMMUNICATION

Parity and Primary Liver Cancer Among Young Women

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Numerous case-control studies conducted in western countries have reported increased risks of primary liver cancer among long-term users (≥ 5 years) of oral contraceptives (1-8). It has been suggested that, in addition to exogenous hormones, endogenous hormones may play a role in the development of this cancer (9). Recently, two studies in European and multinational populations have reported an increased risk of hepatocellular carcinoma with parity (9,10).

Using individuals identified from a nationwide survey of almost 20000 decedents in the United States, we examined in further detail the association of primary liver cancer with number of live births.

The source population for the study subjects has been described in detail in previous publications (8,11). Briefly, the National Mortality Followback Survey (NMFS) identified and obtained death certificates for a representative sample of deaths among U.S. adults. Questionnaires were sent to next of kin to obtain information on lifestyle factors, including number of live births. The response rate for the informant questionnaire was 89%.

As part of the NMFS, all women who died of primary liver cancer (International Classification of Diseases 9th Revision = 155.0) between the ages of 25 and 49 in the United States in 1985 or who were included in a 1% NMFS sample of deaths in 1986 were identified as case subjects. Case subjects

who had a history of liver cirrhosis were excluded from the analysis. Controls were women in the 1986 NMFS survey who died between the ages of 25 and 49 of causes other than liver cancer, liver cirrhosis, chronic liver disease, or oral contraceptive-related conditions (8). The major causes-of-death categories for control subjects were cancer (26%), diseases of the respiratory system (9%), injury (33%), and poisoning (9%).

Odds ratios (ORs) by number of live births were estimated using multiple logistic regression (12). Whenever appropriate, we included in the analysis potential confounding factors, including age at death (5-year intervals), race (White, Black, other), years of education, marital status, a history of hysterectomy or sterilization, cigarette smoking (ever/never), use of alcoholic beverages, and duration of oral contraceptive use (0, 1-4, 5-9, ≥ 10 years).

The risk of primary liver cancer among women who had had a live birth was 1.9 (95% confidence interval [95% CI] = 0.9-4.0) compared with women who had never had a live birth. Table 1 shows that the risk of primary liver cancer rose with number of live births, although the dose-response relationship was neither consistent nor statistically significant. Risks of primary liver cancer were more pronounced when the analysis was restricted to subjects with spouse or parent respondents. All estimates in Table 1 were adjusted for age at death, race, and duration of oral contraceptive use. Additional adjustment for education, marital status, smoking, use of alcoholic beverages, and a history of hysterectomy or tubal ligation had no influence on the risk estimates.

Table 2 shows that the ORs associated with the number of live births were, in general, higher among never-users of oral contraceptives than ever-users. Among oral contraceptive users, however, the risk associated with number of live births was higher among long-term (≥ 5 years) than short-term users, but the numbers were too small to evaluate the joint effect of oral contraceptive exposure and number of live births.

Consistent with findings from studies in intermediate-risk (10) and high-risk (9) areas, our findings indicate that number of live births is positively

related to risk of primary liver cancer in the United States—a low-risk area—which supports the hypothesis that endogenous hormones may play a role in the development of this cancer.

It is unlikely that the observed parity relationship is due to a subset of the control women who died of causes related to fertility problems, since women who died of causes known to be related to oral contraceptive use or fertility were excluded prior to analysis. Furthermore, the excess risk among parous women persisted when the analysis was restricted to control women who died of injury or poisoning.

It was unexpected that the risk of primary liver cancer was more pronounced when the analysis was restricted to subjects with parent or spouse respondents. It is possible that friend or neighbor respondents might provide less accurate information on parity, although there are no data to support a substantial misreporting of parity among these types of respondents.

It is plausible that the risk of primary liver cancer may increase with the number of live births and accompanying changes in endogenous hormones, given that (a) estrogen profiles differ between parous and nulliparous women (13), (b) levels of estrogens increase substantially during pregnancy (14), (c) estrogens affect liver metabolism (15), (d) pregnancy may increase susceptibility to hepatitis and its sequelae (16), and (e) use of exogenous hormones increases the risk of primary liver cancer in low-risk countries (1-8).

Further research is needed to assess the interrelationships between parity, infection with hepatitis B or C virus, and other risk factors for primary liver cancer and to clarify the biological mechanisms involved.

Received April 8, 1992; revised May 13, 1992; accepted May 14, 1992.

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Table 1. ORs for primary liver cancer associated with number of live births

No. of live births	All respondents				Parent or spouse respondents			
	Cases*	Controls*	OR†	95% CI	Cases‡	Controls‡	OR†	95% CI
Total	72	599			50	413		
0	9	142	1.0	—	4	107	1.0	—
≥1	63	457	1.9	0.9-4.0	46	306	3.3	1.1-9.9
1	11	104	1.6	0.6-4.2	7	69	2.5	0.7-9.2
2	24	162	2.1	0.9-4.8	18	114	3.7	1.2-11.9
3	15	99	1.9	0.8-4.7	13	72	3.8	1.1-13.3
4-5	8	74	1.6	0.5-4.5	5	45	2.8	0.6-12.4
≥6	5	18	2.9	0.8-11.2	3	6	5.8	0.7-46.5
Trend test	<i>P</i> = .22				<i>P</i> = .07			

*Does not include four cases and 30 controls with missing data.

†Adjusted for age at death, race, and duration of oral contraceptive use (0, 1-4, 5-9, ≥10 years).

‡Does not include three cases and 18 controls with missing data.

Table 2. ORs for primary liver cancer associated with number of live births by use of oral contraceptives

No. of live births	Never used oral contraceptives				Ever used oral contraceptives			
	Cases*	Controls*	OR†	95% CI	Cases‡	Controls‡	OR†	95% CI
Total	30	293			38	239		
0	4	78	1.0	—	4	48	1.0	—
1	3	53	1.2	0.2-5.7	7	37	1.8	0.5-6.9
2	12	69	3.6	1.1-12.0	11	77	1.3	0.4-4.5
3	6	44	2.2	0.6-9.1	9	47	1.7	0.4-6.4
4-5	3	35	1.9	0.4-9.4	4	26	1.0	0.2-5.0
≥6	2	14	3.6	0.5-26.3	3	4	2.8	0.3-23.5

*Does not include three cases and 13 controls with missing data.

†Adjusted for age at death and race.

‡Does not include one case and four controls with missing data.

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