

# Cigarette smoking and parity as risk factors for the development of symptomatic gall bladder disease in women: results of the Royal College of General Practitioners' oral contraception study

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## Abstract

The effects of cigarette smoking and parity on the development of symptomatic gall bladder disease remain controversial. These relations have been examined in a cohort of 46 000 women followed for up to 19 years during the Royal College of General Practitioners' (RCGP) oral contraception study. During follow up, 1087 women were recorded as experiencing their first ever episode of symptomatic cholelithiasis (International Classification of Diseases, 8th revision (ICD-8) 574) or cholecystitis (ICD-8 575). Smokers were more likely to develop symptomatic gall bladder disease than non-smokers (relative risk 1.19; 95% confidence intervals (95% CI) 1.06 to 1.34) and there was a significant trend with the number of cigarettes smoked daily (test for trend  $\chi^2=7.58$ ,  $p<0.01$ ). This relation was most apparent among never users of oral contraceptives, although similar trends were found among current and former users. A significant direct relation between symptomatic gall bladder disease and parity was also found (test for trend  $\chi^2=21.89$ ,  $p<0.001$ ). When all were examined together a trend of increasing risk with lower social class was also found (test for trend  $\chi^2=5.72$ ,  $p=0.02$ ). Current users of oral contraceptives had a moderately increased risk of symptomatic gall bladder disease (relative risk 1.15; 95% CI 0.99 to 1.34), unlike former users (relative risk 1.03; 95% CI 0.90 to 1.18). These results suggest that smoking and parity are important risk factors for the development of symptomatic gall bladder disease in women.

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It is currently thought that cholesterol gall stones arise because of a triple hepatobiliary defect: cholesterol supersaturation of gall bladder bile, reduction gall bladder contractility, and increased rate of cholesterol nucleation, probably due to mucin glycoprotein hypersecretion.<sup>1,2</sup>

Two recent case-control studies have suggested that smoking might protect against gall stone disease.<sup>3,4</sup> Both found a halving in risk of gall stone disease for smokers compared with non-smokers. Previous reports have indicated, however, that smoking is associated with an increased risk of gall stone disease.<sup>5-7</sup>

Evidence for a positive association between parity and gall bladder disease is also contradictory, notwithstanding many studies of this

relation.<sup>8</sup> Pregnancy could affect each of the processes involved in gall stone formation. For example, progesterone impairs gall bladder contractility,<sup>9</sup> and oestrogens may increase cholesterol saturation of bile<sup>10</sup> and gall bladder prostaglandin synthesis,<sup>11</sup> and thus possibly mucin secretion by the gall bladder mucosa. A previous report from the Royal College of General Practitioners' (RCGP) oral contraception study suggested that the pill accelerated the development of symptomatic gall stone disease in women prone to the disease.<sup>12</sup>

This report has used further data from the RCGP oral contraception study to examine the influence of smoking and parity on the development of gall stone disease.

## Methods

The organisation and methods used in the RCGP study have been described in detail elsewhere.<sup>12</sup> Briefly, over a 14 month period starting in May 1968, 1400 general practitioners throughout the United Kingdom recruited 23 000 women who were using oral contraceptives and a similar number of women who had never used these preparations. The two groups were age matched and all women were married or living as married. Data on smoking habit and social class were collected at recruitment, at which time 48% of pill users smoked compared with 42% of the controls. Social class was based on the occupation of the women's husband. Every six months since recruitment, the general practitioners have supplied information about any use of hormonal preparations including oral contraceptives, any pregnancies, any operations, and all newly presenting episodes of illness. These results relate to data available at April 1987, by which time about 65% of subjects were no longer under observation, mainly because they have moved from the recruiting doctors' practice.

All women who experienced their first ever episode of symptomatic cholelithiasis (International Classification of Diseases, 8th revision (ICD-8 code 574) or cholecystitis (ICD-8 code 575) were included in this analysis. For the 108 women with both conditions, only the first episode was counted. The diagnosis was that given by the reporting general practitioner, and each event was categorised according to the woman's contraceptive state at the time of the event. Events occurring during pregnancy were excluded, together with the related periods of observation.

The incidence rates were indirectly standard-

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TABLE I Crude and standardised rates (per 1000) of reported first episode of gall bladder disease (ICD-8 574 or 575) by use of oral contraceptives and age

Age at diagnosis (y)	Never users		Former users		Current users		All women	
	Crude rate (No)	Standardised rate*	Crude rate (No)	Standardised rate*	Crude rate (No)	Standardised rate*	Crude rate (No)	Standardised rate
<24	1.37 (12)	1.62	1.02 (4)	1.16	1.69 (22)	1.92	1.48 (38)	1.67
25-	2.81 (66)	3.08	2.43 (33)	2.46	2.55 (63)	2.58	2.62 (162)	2.70
30-	1.95 (65)	2.04	2.12 (56)	2.05	2.65 (73)	2.57	2.22 (194)	2.20
35-	2.19 (84)	2.25	2.21 (81)	2.12	3.00 (64)	2.86	2.38 (229)	2.35
40-	2.06 (71)	2.10	2.72 (88)	2.58	2.52 (33)	2.38	2.40 (192)	2.36
45-	2.81 (68)	2.86	3.56 (82)	3.34	3.32 (17)	3.14	3.19 (167)	3.14
50-	2.82 (36)	2.86	3.00 (39)	2.83	8.52 (5)	8.22	3.04 (80)	3.00
>50	2.12 (13)	2.14	2.20 (12)	2.09	— (0)	—	2.16 (25)	2.15
All women	2.29 (415)	2.35	2.56 (395)	2.43	2.63 (277)	2.70		
Women - years of observation	181 475		154 480		105 412		441 367	

\*Standardised for social class and smoking at recruitment and parity at time of the diagnosis. Observed numbers in parentheses.

used for age and parity at diagnosis and social class at recruitment, with the total study population as the reference population. All rates quoted are per 1000 women-years. The method of indirect standardisation involved applying stratum specific rates from the total cohort to the person-years of observation in the relevant stratum of each contraceptive group. These expected numbers were used to weight the observed incidence rates.<sup>12</sup> Confidence intervals were calculated on the assumption that the variance of the log relative risk is equal to the sum of the reciprocals of the observed number of cases in the two groups being compared. Test for linear trends were based on Mantel's method<sup>13</sup> modified to accommodate standardised data.

### Results

A total of 1087 women had a diagnosis of symptomatic gall bladder disease (cholelithiasis (ICD-8 574) or cholecystitis (ICD-8 575)). The rate of gall bladder disease was not affected by age (Table I).

### SMOKING

Women who smoked were significantly more likely to be diagnosed as having gall bladder disease; rate 2.26 per 1000 women-years among non-smokers, 2.69 per 1000 women-years among moderate smokers (1-15 cigarettes per day), and 2.74 per 1000 women-years in heavy smokers ( $\geq 16$  cigarettes per day) (test for trend:  $\chi^2=7.58$ ,  $p<0.01$ ) (Table II). The relative risk for all smokers compared with non-smokers was 1.19 (95% confidence intervals (95% CI) 1.06 to 1.34). Higher rates of symptomatic gall bladder

disease were seen among smokers in each oral contraceptive group, although the trend was only significant for never users of the pill.

### PARITY

A clear trend of increasing risk with increasing parity was seen in each of the oral contraceptive groups (Table III). The rate of symptomatic gall bladder disease among women of parity 1 was generally twice that of their nulliparous counterparts.

### SOCIAL CLASS

When all women were examined together, there was a significant trend of increasing risk of gall bladder disease with lower social class. Similar trends were found in each of the contraceptive groups, although these did not reach statistic significance (Table IV).

### ORAL CONTRACEPTIVE USE

Compared with never users the relative risk of symptomatic gall bladder disease in current users was 1.15 (95% CI 0.99 to 1.34), and in former users 1.03 (95% CI 0.90 to 1.18).

### Discussion

The results of this longterm prospective study suggest that cigarette smoking, parity, and possibly lower social class are important risk factors for the development of symptomatic gall bladder disease in women. The overall incidence of symptomatic gall stones among the 20 819 women who said they were smokers at the start of

TABLE II Crude and standardised rates (per 1000) of reported first episode of gall bladder disease (ICD-8 574 or 575) by use of oral contraceptives and smoking habits

	Never users		Former users		Current users		All women	
	Crude rate (No)	Standardised rate*	Crude rate (No)	Standardised rate*	Crude rate (No)	Standardised rate*	Crude rate (No)	Standardised rate
Smoking habits at recruitment (cigarettes daily):								
0	2.04 (224)	2.11	2.36 (191)	2.29	2.37 (129)	2.51	2.22 (544)	2.26
1-15	2.60 (149)	2.62	2.80 (157)	2.63	2.85 (111)	2.95	2.73 (417)	2.69
$\geq 16$	2.91 (42)	2.83	2.69 (47)	2.48	3.06 (37)	3.06	2.86 (126)	2.74
Test for trend	$\chi^2=5.58$ , $p<0.02$		$\chi^2=0.92$ , $p>0.05$		$\chi^2=1.86$ , $p>0.05$		$\chi^2=7.58$ , $p<0.01$	
Relative risk: Smokers/non-smokers (95% CI)	1.26 (1.04 to 1.53)		1.13 (0.93 to 1.38)		1.19 (0.94 to 1.51)		1.19 (1.06 to 1.34)	

\*Standardised for social class at recruitment, age and parity at diagnosis. Observed numbers in parentheses.

TABLE III Crude and standardised rates (per 1000) of reported first episode of gall bladder disease (ICD-8 574 or 575) by use of oral contraceptives and parity

	Never users		Former users		Current users		All women	
	Crude rate (No)	Standardised rate*	Crude rate (No)	Standardised rate*	Crude rate (No)	Standardised rate*	Crude rate (No)	Standardised rate
Parity at diagnosis:								
0	1.20 (23)	1.24	1.45 (9)	1.53	0.40 (3)	0.48	1.06 (35)	1.17
1	2.29 (76)	2.34	1.68 (28)	1.68	2.99 (47)	3.31	2.30 (151)	2.43
2+3	2.32 (245)	2.33	2.50 (255)	2.44	2.69 (182)	2.80	2.48 (682)	2.48
≥4	3.01 (71)	2.81	3.49 (103)	3.17	3.08 (45)	2.97	3.24 (219)	2.96
Test for trend	$\chi^2=3.88, p<0.05$		$\chi^2=12.27, p>0.01$		$\chi^2=9.15, p<0.01$		$\chi^2=21.89, p<0.01$	

\*Standardised for social class and smoking at recruitment and age at diagnosis. Observed numbers in parentheses.

the study was 20% higher than that found among the 25 558 non-smokers. The relation with smoking was most apparent in those women who had never used oral contraception. The rate of symptomatic gall bladder disease roughly doubled once a woman had been pregnant. Women in social classes IV+V had a 25% greater risk of symptomatic gall bladder disease compared with those in social classes I+II.

The validity of these findings needs careful consideration. This study assessed symptomatic gall bladder disease rather than the total occurrence of the condition. It is likely, however, that symptom free and symptomatic gall bladder disease share a common pathogenesis and thus we believe it remains valid to examine factors that predict symptomatic episodes of the illness.

The data are based on reports supplied by the participating general practitioners. Although about 20% of the women were taken into hospital at the time of their illness, we do not know how many of the episodes were confirmed radiologically or at operation. This apparent lack of confirmatory evidence would be important if the general practitioners diagnosed gall bladder disease differently among patients with particular characteristics – for instance, if they made the diagnosis more often in smokers than non-smokers. Although possible, we think it unlikely for this to have occurred for risk factors such as smoking and parity. On the other hand it is possible that such a diagnostic suspicion bias accounts for the modest increase in risk among current users but not former users of the pill, although previous work has suggested that this pattern of risk may be due to an accelerating effect of the pill.<sup>14</sup>

By 1987 about 65% of the women were no longer under observation, mainly because they had moved from the recruiting doctors' practice area. These women were more likely to be younger, of higher social class, and lower parity than those still in the study, but their smoking habits at recruitment were no different. Further-

more, the characteristics of pill users no longer observed were similar to never users no longer observed, so comparison between contraceptive groups also remains valid. The smoking data have not been updated since recruitment. Many of the women will have stopped and few will have started smoking. Resulting misclassification will tend to dilute the effect of smoking and so our risk estimates are likely to be underestimates.

We were not able to adjust for the possible confounding effect of body weight as this information has not been collected. A direct relation between body mass index and the risk of gall bladder disease has been described.<sup>15</sup> Another cohort study has found that pill users tend to be slightly lighter than non-users.<sup>16</sup> It seems unlikely, therefore, that the ability to adjust for body weight would have materially affected the results that relate to pill use. Also, because smoking tends to be associated with a lower body mass index, our inability to adjust for any confounding due to body weight will have tended to result in an underestimation of the effect of smoking.

Previous studies of the effect of smoking on gall bladder disease have reported conflicting results. The Framingham population cohort study found that compared with non-smokers, those who smoked had a lower rate of clinical gall bladder disease, a difference that reached borderline statistical significance.<sup>17</sup> The authors were unable, however, to correct for confounding other than by age and sex. Smoking was also found to be associated with a substantial protective effect in a case-control study of symptomatic gall bladder disease, and in a recent case-control study of patients undergoing cholecystectomy.<sup>3,4</sup> In both of these studies the control group, hospital inpatients and community controls, had unusually high smoking rates.<sup>3,4</sup> Interpretation is therefore problematic.

By contrast, three other studies have found a positive association between cigarette smoking and gall bladder disease. Petitti *et al* found a

TABLE IV Crude and standardised rates (per 1000) of reported first episode of gall bladder disease (ICD-8 574 or 575) by use of oral contraceptives and social class

	Never users		Former users		Current users		All women	
	Crude rate (No)	Standardised rate*	Crude rate (No)	Standardised rate*	Crude rate (No)	Standardised rate*	Crude rate (No)	Standardised rate
Social class at recruitment:								
I+II	1.99 (85)	2.07	2.50 (83)	2.40	2.14 (50)	2.26	2.20 (218)	2.22
III	2.34 (234)	2.42	2.30 (205)	2.19	2.68 (160)	2.75	2.40 (599)	2.41
IV+V	2.48 (91)	2.49	3.21 (97)	2.96	2.97 (60)	2.95	2.84 (248)	2.77
Test for trend	$\chi^2=2.52, p<0.05$		$\chi^2=2.09, p<0.05$		$\chi^2=1.92, p>0.05$		$\chi^2=5.72, p<0.02$	

\*Standardised for social class at recruitment age, and parity at diagnosis. Excludes 22 women whose social class was unknown; observed numbers in parentheses.

statistically significant increased risk of clinical gall bladder disease among smokers in a case control study of female twins<sup>7</sup> and Layde *et al* found an increased risk in a cohort study of women attending British family planning clinics.<sup>18</sup> The third study found a direct relation between smoking and clinical gall bladder disease among men but not among women.<sup>6</sup>

Two large population surveys with ultrasound to detect gall bladder disease have also shown an increase in the overall prevalence of gall bladder disease among male but not female smokers, although the findings were not clear cut.<sup>19,20</sup> For example, the increased risk found by Jorgensen showed only a weak dose response relation,<sup>19</sup> and the effect found by the Rome Group for Epidemiology and Prevention of Cholelithiasis was reduced after adjustments for confounding factors.<sup>20</sup>

On balance the better controlled studies have shown that cigarette smoking promotes gall bladder disease. At present, we do not know how smoking might promote either gall stone formation or the development of symptoms. Smoking could affect gall bladder pathophysiology – for example, by stimulating mucin secretion and thus promoting cholesterol monohydrate nucleation – a critical step in gall stone formation.<sup>21</sup> Certainly smoking stimulates mucin secretion by the respiratory tract mucosa, probably by a direct irritant effect. Recent evidence suggests, however, that nicotine inhibits gall bladder bile mucin concentration.<sup>22</sup> Alternatively, smoking could exert an effect on gall bladder contractility, possibly by inhibition of prostaglandin synthesis. There is, however, conflicting evidence regarding the effect of inhibitors of prostaglandin synthesis on gall bladder contractility.<sup>23,24</sup>

Interest in whether parity and the use of oral contraceptives are associated with the development of symptomatic gall bladder disease has been stimulated by the consistent finding that women of reproductive age have a higher incidence of symptomatic and symptom free gall bladder disease compared with men of the same age. Previous reports have found that parity did not increase the risk of symptomatic gall bladder disease, increased the risk after a single pregnancy, or only increased the risk after several pregnancies. Thijs and colleagues recently reviewed the results of all controlled studies on this issue and noted that a statistically significant positive association between parity or pregnancy was found in 26 of 42 studies.<sup>8</sup> Nevertheless, the most recent large epidemiological study to consider this issue, the American Nurses Health study found no relation between parity and the development of clinical gall stone disease.<sup>25</sup> Inconsistencies in the results of previous studies may be due to variations in the level of symptom recall, patient complaint, or consultation with medical practitioners and type of investigation performed on the various study populations. An alternative explanation might be that pregnancy increases the risk of gall stone formation only transiently. Thijs *et al* have postulated that pregnancy exerts an effect that disappears after about five years.<sup>8</sup> Some studies they suggest may have failed to detect an effect of

parity because they did not concentrate on this risk period.<sup>8</sup>

Pregnancy is often associated with two definite gall bladder abnormalities – namely, reduced gall bladder contractility, which is believed to be due to raised progesterone concentrations, and the development of biliary sludge.<sup>8</sup> Biliary sludge contains cholesterol crystals, calcium bilirubinate granules, and very high concentrations of mucin glycoprotein, a putative nucleating agent.<sup>26</sup> Many studies suggest that sludge formation is a marker of gall stone formation. A recent Italian study showed that during pregnancy or the puerperium 41% of women develop biliary sludge.<sup>27</sup> Progression to gall stone formation in a sizeable proportion of these subjects may be the mechanism whereby pregnancy predisposes to gall stone formation.

Early studies of the effects of oral contraceptives suggested that the pill was associated with a large increase in risk of symptomatic gall bladder disease.<sup>28</sup> Most recent studies have, however, failed to confirm this. Scragg *et al* in a case-control study found that ever use of the pill was associated with an increased risk of symptomatic gall bladder disease in women younger than 29 years and a reduced risk of symptomatic gall bladder disease in older women.<sup>29</sup> We were unable to find such a relation. Our results suggest that at most, current use of the pill is associated with only a small increase in risk of clinical gall bladder disease, which disappears after stopping the pill. If it is not due to diagnostic suspicion bias then postulated mechanisms might include changes in gall bladder contractility associated with the progesterone content,<sup>9</sup> or increased cholesterol saturation of bile due to the oestrogen content.<sup>10</sup>

In summary, cigarette smoking, parity, and possibly lower social class were associated with an increased risk of symptomatic gall bladder disease in women. The effect of smoking was most apparent in those who had never used oral contraception. Use of the oral contraceptive pill was associated with a small increase in risk that was limited to current users.

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