Mortality associated with oral contraceptive use: 25 year follow up of cohort of 46 000 women from Royal College of General Practitioners' oral contraception study

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Abstract

Objective To describe the long term effects of the use of oral contraceptives on mortality.
Design Cohort study with 25 year follow up. Details of oral contraceptive use and of morbidity and mortality were reported six monthly by general practitioners. 75% of the original cohort was "flagged" on the NHS central registers.
Setting 1400 general practices throughout Britain.
Subjects 46 000 women, half of whom were using oral contraceptives at recruitment in 1968-9. Median age at end of follow up was 49 years.
Main outcome measures Relative risks of death adjusted for age, parity, social class, and smoking.
Results Over the 25 year follow up 1599 deaths were reported. Over the entire period of follow up the risk of death from all causes was similar in ever users and never users of oral contraceptives (relative risk = 1.0, 95% confidence interval 0.9 to 1.1; P = 0.7) and the risk of death for most specific causes did not differ significantly in the two groups. However, among current and recent (within 10 years) users the relative risk of death from ovarian cancer was 0.2 (0.1 to 0.8; P = 0.01), from cervical cancer 2.5 (1.1 to 6.1; P = 0.04), and from cerebrovascular disease 1.9 (1.2 to 3.1, P = 0.009). By contrast, for women who had stopped use ⩾10 years previously there were no significant excesses or deficits either overall or for any specific cause of death.
Conclusion Oral contraceptives seem to have their main effect on mortality while they are being used and in the 10 years after use ceases. Ten or more years after use ceases mortality in past users is similar to that in never users.

Introduction

Oral contraceptives have been available for 40 years and, although their short term effects on health have been studied in detail,[1 2] comparatively little is known about whether these effects persist after use stops. The Royal College of General Practitioners' oral contraception study was set up in 1968 to monitor the health of women who had used oral contraceptives. We present the results of a 25 year follow up of that population examining the effect of use of oral contraceptives on mortality in the long term.

Subjects and methods

Over 14 months from May 1968, 1400 general practitioners throughout the United Kingdom recruited 23 000 women who were using oral contraceptives and a similar number who had never used them into the oral contraception study.[1] Most women (98%) were white and all were married or living as married. General practitioners were asked to provide information on oral contraceptives prescribed, pregnancies, new illness, or death for each subject every six months. During the early years of the study some general practitioners withdrew their patients and some women moved and left the study. In 1976-7 an attempt was made to "flag" the cohort on the NHS central registers in Southport and Edinburgh to provide information on death and cause of death for women who were no longer being followed regularly by their general practitioner. About 75% of the original cohort was successfully flagged, and these women have been followed for death and emigration since then. The remaining 25% could not be flagged because they or their general practitioners had left the study before the flagging procedure could be instigated and the personal details required for flagging were not available to the investigators. The mortality of the women who were followed regularly by their general practitioner was similar to that of women who left the study.[3]

This analysis includes deaths up to 31 December 1993. We obtained a copy of the death certificate for all women who had died, and CK or PH coded the cause of death according to ICD-8 (international classification of diseases, eighth revision),[4] occasionally supplementing information from the death certificate with details provided by general practitioners.[5] Person-years of follow up were calculated from the date of recruitment up to the date of death for the 1599 women who had died, up to the date of last contact with the general practitioner for 10 958 women who were not flagged on the NHS registers, or up to 31 December 1993 for 33 554 women who were flagged on the NHS registers and alive on that date.[3] For women who were no longer being followed by their general practitioner before 1 January 1977 but were

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flagged no person-years were included for the period between the date of last contact with their general practitioner and 1 January 1977 because the ascertainment of deaths during that period may have been incomplete.[3]

Person-years were categorised by age (16-19, 20-24…70-79), parity (0, 1-2, ≥3, not known), social class at recruitment (I-II, III, IV-V, other), and cigarette smoking at recruitment (0, 1-14/day, ≥15/day, not known) with a standard computer program.[6] Person-years were further subdivided according to whether the women had taken oral contraceptives and, where appropriate, by duration of use and time since first and last use. At recruitment half (23 000) of the subjects were using oral contraceptives, but by 31 December 1993, 63% had used them at some time. Women who started using oral contraceptives after recruitment contributed person-years to the "never user" category up to the date that they began using them. For women who were flagged on the NHS registers but no longer regularly followed up by their general practitioner, we assumed that past users and never users who were over the age of 40 at the date of last contact did not subsequently take oral contraceptives. For current users and women aged under 40 at the time of last contact with their general practitioners, we assumed that use continued for two years as stated at the time of last contact, but thereafter use was classified as unknown. These assumptions about subsequent use of oral contraceptives are similar to those used in analyses of other cohort studies.[7]

The results presented here are based on 853 517 person-years of follow up until 31 December 1993: 517 519 in women who had used oral contraceptives and 335 998 in women who had never used them. Standardised mortality ratios were calculated by using mortality for women in England and Wales as a standard.[6] Relative risks were adjusted for age, parity, social class, and smoking with the Poisson regression program module of EPICURE.[8] P values are two tailed.

Results

By 31 December 1993 the cohort had been followed for 25 years and the median age of the women was 49 years (48 for ever users of oral contraception and 50 for never users). During that period 1599 deaths were reported, 945 in ever users and 654 in never users (table 1). The death rate from all causes combined was 21% lower than in the UK population (overall standardised mortality ratio = 79). The relative risk of death from all causes combined after adjustment for age, parity, social class, and cigarette smoking did not differ significantly between ever users and never users (relative risk = 1.0, 95% confidence interval 0.9 to 1.1; P = 0.7).

Table 1 also shows standardised mortality ratios and adjusted relative risks of death for common specific causes and groups of causes of death (and also for some particular causes that have been reported to be affected by oral contraceptive use) according to ever use of oral contraceptives. For most specific causes of death the standardised mortality ratios in ever users and never users of oral contraceptives were around 100 and did not differ significantly between the two groups. The few exceptions were colorectal cancer and ovarian cancer, for which the relative risks of death in users were significantly below 1.0, and cerebrovascular disease and all violent and accidental causes of death, for which the relative risks were significantly greater than 1.0. Ever use is, however, a crude measure of use of oral contraceptives.

Table 1 Standardised mortality ratios in ever users and never users of oral contraceptives and relative risk in ever users compared with never users

Cause of death (ICD-8 code)	Standardised mortality ratio (No of deaths)		Relative risk† (95% CI)
	Ever users	Never users	
All causes (000-999)	82 (945)	74 (654)	1.0 (0.9 to 1.1)
All cancers (140-209)	85 (474)	85 (355)	1.0 (0.8 to 1.1)
Colorectal (153-154)	62 (29)	108 (39)	0.6 (0.4 to 0.9)*
Liver (155)	126 (5)	34 (1)	5.0 (0.6 to 43.2)
Lung (162)	107 (75)	71 (40)	1.2 (0.8 to 1.8)
Breast (174)	87 (154)	81 (105)	1.1 (0.8 to 1.4)
Cervix (180)	115 (38)	57 (13)	1.7 (0.9 to 3.2)
Uterus (181-2)	22 (2)	83 (6)	0.3 (0.1 to 1.4)
Ovary (183)	49 (24)	83 (31)	0.6 (0.3 to 1.0)*
Other cancers	87 (147)	95 (120)	0.9 (0.7 to 1.1)
All circulatory diseases (390-458)	84 (237)	63 (143)	1.2 (1.0 to 1.5)
Ischaemic heart disease (410-4)	70 (98)	68 (79)	0.9 (0.7 to 1.3)
Other heart disease (420-9)	107 (19)	66 (9)	1.4 (0.6 to 3.1)
Cerebrovascular disease (430-8)	111 (87)	62 (38)	1.5 (1.0 to 2.3)*
Other circulatory	73 (33)	46 (17)	1.4 (0.8 to 2.5)
All digestive diseases (520-77)	85 (37)	74 (24)	1.1 (0.6 to 1.8)
Liver disease (570-3)	112 (23)	69 (10)	1.7 (0.8 to 3.6)
All other diseases (1-139, 210-389, 460-519, 578-799)	53 (95)	65 (89)	0.8 (0.6 to 1.0)
Violent or accidental causes (800-999)	111 (102)	68 (43)	1.6 (1.1 to 2.3)*
Suicide (950-9)	123 (39)	73 (16)	1.5 (0.8 to 2.7)

*P<0.05. †Adjusted for age, social class, parity, and smoking.

Table 2 shows for various causes the relative risk of death compared with never users in relation to the number of years since oral contraceptives were first used. Within the first 10 years of starting use of oral contraceptives there was a significant excess mortality from all causes of death (relative risk = 1.2, 95% confidence interval 1.0 to 1.50; P = 0.03), all circulatory diseases (2.2, 1.5 to 3.2; P < 0.0001), and cerebrovascular disease (2.7, 1.5 to 4.9; P = 0.0008). However, the excess mortality from these causes fell with time, this trend being significant for all circulatory disease (P = 0.002) and cerebrovascular disease (P = 0.02). There were 380 deaths in women who began using oral contraceptives more than 20 years before the end of follow up, and this group showed no significant excess or deficit in mortality from any specific condition or overall.

Table 3 shows the pattern of risk of death for various conditions in relation to the time since stopping use of oral contraceptives. By the end of follow up the median time since last use in the cohort was 17 years. Significant increases or decreases in risk were found mainly in current users or those who had stopped use within the past 10 years—for example, women who were current users or who stopped use in the past five years had a significantly reduced risk of ovarian cancer (0.1, 0.0 to 0.9; P = 0.04) and a significant excess of all circulatory diseases (1.7, 1.2 to 2.4; P = 0.006) and cerebrovascular disease (1.9, 1.1 to 3.4; P = 0.03) and women who had stopped use five to nine years previously had an significant excess risk of cervical cancer (3.0, 1.1 to 8.1; P = 0.03) and cerebrovascular disease (2.0, 1.1 to 3.7; P = 0.02). Among women who had stopped use 15 or more years previously most of

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Table 2 Relative risk of death in users of oral contraceptives compared with never users according to time since first use

Cause of death (ICD-8 code)	Years since first use of oral contraceptives						(P value) test for trend by time since first use
	<10		10-19		⩾20		
	Relative risk† (95% CI)	No of deaths	Relative risk† (95% CI)	No of deaths	Relative risk† (95% CI)	No of deaths	
All causes (000-999)	1.2 (1.0 to 1.5)*	167	1.1 (0.9 to 1.2)	398	0.9 (0.8 to 1.1)	380	0.09
All cancers (140-209)	0.9 (0.7 to 1.3)	61	1.0 (0.8 to 1.2)	212	0.9 (0.8 to 1.1)	201	0.6
Colorectal (153-154)	0.7 (0.2 to 2.2)	4	0.5 (0.3 to 1.1)	11	0.6 (0.3 to 1.1)	14	0.8
Lung (162)	0.9 (0.3 to 2.3)	5	1.3 (0.8 to 2.1)	34	1.2 (0.7 to 1.9)	36	0.8
Breast (174)	1.1 (0.7 to 1.8)	22	1.2 (0.9 to 1.6)	74	1.0 (0.7 to 1.3)	58	0.8
Cervix (180)	0.8 (0.3 to 2.5)	5	2.0 (1.00 to 4.0)	22	1.8 (0.8 to 4.2)	11	0.2
Ovary (183)	0.9 (0.3 to 2.7)	4	0.5 (0.2 to 1.0)*	8	0.6 (0.3 to 1.3)	12	0.8
Other cancers	1.0 (0.6 to 1.6)	21	0.9 (0.7 to 1.2)	63	0.9 (0.7 to 1.2)	70	0.4
All circulatory diseases (390-458)	2.2 (1.5 to 3.2)**	49	1.3 (1.0 to 1.7)	99	0.9 (0.7 to 1.2)	89	0.002
Ischaemic heart disease (410-414)	1.8 (1.0 to 3.2)	14	1.0 (0.7 to 1.6)	41	0.8 (0.5 to 1.1)	43	0.02
Other heart disease (420-429)	2.1 (0.5 to 9.3)	3	1.7 (0.6 to 4.5)	8	1.1 (0.4 to 3.0)	8	0.7
Cerebrovascular disease (430-438)	2.7(1.5 to 4.9)**	23	1.7 (1.1 to 2.7)*	39	1.0 (0.6 to 1.8)	25	0.02
Other circulatory	2.4 (0.9 to 6.5)	9	1.2 (0.6 to 2.7)	11	1.2 (0.6 to 2.5)	13	0.9
All digestive diseases (520-577)	1.2 (0.5 to 3.0)	7	1.3 (0.7 to 2.4)	18	0.9 (0.4 to 1.8)	12	0.9
Liver disease (570-573)	2.0 (0.6 to 7.0)	4	1.5 (0.6 to 3.7)	9	1.8 (0.7 to 4.4)	10	0.7
All other diseases (1-139, 210-389, 460-519, 578-799)	0.9 (0.5 to 1.6)	16	0.6 (0.4 to 0.9)*	28	0.9 (0.6 to 1.3)	51	0.4
Violent and accidental causes (800-999)	1.6 (1.0 to 2.7)	34	1.5 (1.0 to 2.3)	41	1.6 (1.0 to 2.7)	27	0.9
Suicide (950-959)	1.9 (0.9 to 4.1)	16	1.4 (0.7 to 2.8)	17	1.1 (0.4 to 2.9)	6	0.2

*P<0.05,**P<0.01. †Adjusted for age, parity, social class, and smoking.

the relative risks were around 1.0. For ovarian cancer there was a weak suggestion that the protective effect associated with current or recent use wore off (test for trend, P = 0.05).

Among ever users of oral contraceptives, the average duration of use was five years. Table 4 shows the relative risk of death in relation to the duration of use of oral contraceptives. Women who used oral contraceptives for 10 or more years had a significant excess mortality from lung cancer (2.0, 1.1 to 3.5; P = 0.02) and cervical cancer (4.1, 1.6 to 10.6; P = 0.003). The excess deaths from lung cancer were mainly among smokers (17 deaths in smokers and three in non-smokers), the relative risk associated with 10 or more years of use of oral contraceptives being 2.0 for smokers and 2.2 for non-smokers. This excess may be a chance finding or perhaps due to residual confounding. There was also a significant trend of increasing mortality for all cancers combined and for cervical cancer in relation to duration of use (P = 0.02 and 0.03, respectively).

Duration of use and time since first and last use of oral contraceptives were highly correlated, with current and recent users being more likely to have used contraceptives for longer. Table 5 shows the relative risk of death among ever users of oral contraceptives according to time since last use of oral contraceptives and duration of use. All significant results were confined to women currently using oral contraceptives or who had stopped in the past 10 years, although

Table 3 Relative risk of death in users of oral contraceptives compared with never users according to time since last use

Cause of death (ICD-8 codes)	Years since last use of oral contraceptives								(P value) test for trend by time since last use
	Current and <5		5-9		10-14		⩾15		
	Relative risk† (95% CI)	No of deaths	Relative risk† (95% CI)	No of deaths	Relative risk† (95% CI)	No of deaths	Relative risk† (95% CI)	No of deaths	
All causes (000-999)	1.0 (0.9 to 1.2)	199	1.1 (0.9 to 1.3)	142	1.1 (0.9 to 1.3)	189	0.9 (0.8 to 1.1)	196	1.0
All cancers (140-209)	0.9 (0.7 to 1.1)	81	1.1 (0.8 to 1.4)	79	1.1 (0.8 to 1.3)	104	0.9 (0.7 to 1.1)	99	0.9
Colorectal (153-154)	0.5 (0.2 to 1.4)	4	0.6 (0.2 to 1.6)	4	0.2 (0.1 to 0.8)*	2	1.0 (0.5 to 2.0)	12	0.1
Lung (162)	0.8 (0.3 to 1.7)	8	1.1 (0.6 to 2.2)	11	1.3 (0.8 to 2.4)	19	1.2 (0.6 to 2.1)	18	0.9
Breast (174)	1.0 (0.6 to 1.6)	28	1.5 (1.0 to 2.2)	31	1.3 (0.8 to 1.9)	33	0.9 (0.6 to 1.5)	25	0.8
Cervix (180)	2.2 (0.8 to 6.1)	9	3.0 (1.1 to 8.1)*	8	1.6 (0.5 to 4.9)	5	0.7 (0.1 to 3.2)	2	0.3
Ovary (183)	0.1 (0.0 to 0.9)*	1	0.3 (0.1 to 1.4)	2	0.7 (0.3 to 1.8)	6	0.7 (0.3 to 1.7)	6	0.05
Other cancers	1.0 (0.6 to 1.6)	31	0.9 (0.6 to 1.4)	23	1.1 (0.7 to 1.6)	39	0.8 (0.6 to 1.2)	36	0.4
All circulatory diseases (390-458)	1.7 (1.2 to 2.4)**	56	1.4 (0.9 to 2.0)	36	1.2 (0.8 to 1.7)	45	1.0 (0.7 to 1.4)	52	0.2
Ischaemic heart disease (410-414)	1.5 (0.8 to 2.8)	17	0.7 (0.3 to 1.4)	9	1.0 (0.6 to 1.6)	19	1.0 (0.6 to 1.6)	30	0.6
Other heart disease (420-429)	2.4 (0.6 to 9.7)	4	3.0 (0.9 to 10.7)	4	0.7 (0.2 to 3.4)	2	1.0 (0.3 to 3.0)	5	0.3
Cerebrovascular disease (430-438)	1.9 (1.1 to 3.4)*	26	2.0 (1.1 to 3.7)*	18	1.4 (0.8 to 2.6)	16	1.0 (0.5 to 1.9)	13	0.2
Other circulatory	1.8 (0.6 to 4.9)	9	1.7 (0.6 to 4.9)	5	1.8 (0.7 to 4.3)	8	0.1 (0.2 to 2.2)	4	0.6
All digestive diseases (520-577)	1.1 (0.4 to 2.7)	8	1.1 (0.4 to 2.9)	5	1.4 (0.6 to 3.3)	8	0.8 (0.3 to 2.1)	5	0.4
Liver disease (570-573)	1.3 (0.4 to 4.6)	4	2.0 (0.6 to 6.9)	4	1.8 (0.5 to 6.1)	4	1.7 (0.5 to 5.8)	4	0.5
All other diseases (1-139,210-389, 460-519, 578-799)	0.6 (0.3 to 1.1)	19	0.6 (0.3 to 1.1)	10	0.8 (0.5 to 1.3)	19	0.8 (0.5 to 1.3)	28	0.4
Violent and accidental causes (800-999)	1.3 (0.8 to 2.1)	35	1.3 (0.7 to 2.6)	12	1.5 (0.8 to 2.8)	13	1.5 (0.8 to 3.1)	12	0.6
Suicide (950-959)	1.4 (0.6 to 3.0)	16	1.5 (0.6 to 3.9)	6	1.2 (0.4 to 3.7)	4	1.2 (0.3 to 4.5)	3	0.7

*P<0.05, **P<0.01. †Adjusted for age, parity, social class, and smoking.

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Table 4 Relative risk of death in users of oral contraceptives compared with never users according to duration of use

Cause of death (ICD-8 code)	Duration of oral contraceptive use (years) <5 Relative risk† (95% CI)	<5 No of deaths	5-9 Relative risk† (95% CI)	5-9 No of deaths	≥10 Relative risk† (95% CI)	≥10 No of deaths	(P value) test for trend with duration of use
All causes (000-999)	1.0 (0.9 to 1.1)	359	1.0 (0.9 to 1.2)	226	1.1 (0.9 to 1.3)	141	0.2
All cancers (140-209)	0.9 (0.7 to 1.1)	167	0.9 (0.7 to 1.1)	108	1.3 (1.0 to 1.6)	88	0.02
Colorectal (153-154)	0.6 (0.3 to 1.2)	11	0.8 (0.4 to 1.6)	9	0.3 (0.1 to 1.2)	2	0.6
Lung (162)	1.1 (0.6 to 1.8)	25	0.7 (0.4 to 1.4)	11	2.0 (1.1 to 3.5)*	20	0.1
Breast (174)	1.1 (0.8 to 1.6)	58	1.0 (0.7 to 1.5)	33	1.4 (0.9 to 2.1)	26	0.4
Cervix (180)	1.3 (0.5 to 3.4)	9	1.4 (0.5 to 4.0)	6	4.1 (1.6 to 10.6)**	9	0.03
Ovary (183)	0.5 (0.2 to 1.2)	8	0.6 (0.3 to 1.5)	6	0.2 (0.0 to 1.3)	1	0.5
Other cancers	0.8 (0.6 to 1.1)	56	1.0 (0.7 to 1.4)	43	1.2 (0.8 to 1.8)	30	0.1
All circulatory diseases (390-458)	1.2 (0.9 to 1.6)	95	1.3 (1.0 to 1.8)	66	1.0 (0.7 to 1.6)	28	0.6
Ischaemic heart disease (410-414)	1.0 (0.7 to 1.6)	38	1.0 (0.7 to 1.7)	25	0.8 (0.5 to 1.6)	12	0.6
Other heart disease (420-429)	1.2 (0.4 to 3.3)	7	2.1 (0.8 to 5.7)	7	0.5 (0.1 to 4.2)	1	1.0
Cerebrovascular disease (430-438)	1.5 (0.9 to 2.3)	35	1.7 (1.0 to 2.9)*	27	1.3 (0.7 to 2.6)	11	0.9
Other circulatory	1.5 (0.7 to 3.2)	15	1.2 (0.5 to 3.0)	7	1.4 (0.4 to 4.2)	4	0.8
All digestive diseases (520-577)	1.1 (0.5 to 2.2)	14	0.9 (0.4 to 2.2)	7	1.2 (0.4 to 3.3)	5	1.0
Liver disease (570-573)	1.4 (0.5 to 3.8)	7	1.4 (0.4 to 4.7)	4	3.0 (1.0 to 9.5)	5	0.3
All other diseases (1-139, 210-389, 460-519, 578-799)	0.8 (0.5 to 1.1)	41	0.8 (0.5 to 1.2)	25	0.5 (0.3 to 1.1)	10	0.6
Violent and accidental causes (800-999)	1.4 (0.9 to 2.1)	42	1.3 (0.8 to 2.3)	20	1.4 (0.7 to 2.9)	10	0.9
Suicide (950-959)	1.1 (0.5 to 2.4)	14	1.8 (0.8 to 3.9)	11	1.4 (0.5 to 4.5)	4	0.4

*P<0.05, **P<0.01. †Adjusted for age, parity, social class, and smoking.

among such women duration of use was not associated with a significant increase or decrease in mortality from any particular cause or overall. Women who stopped using oral contraceptives 10 or more years previously had no significant increases or decreases in relative risk of death from any cause, even if they had used them for 10 years or more. There were, however, only 54 deaths in this subgroup.

Discussion

Our results suggest that most of the effects of oral contraceptives on mortality occur in current or recent users and that few, if any, effects persist 10 years after stopping use. These results relate predominately to use of combined oral contraceptives containing 50 µg oestrogen.[1]

Information on use of oral contraceptives was recorded prospectively at six monthly intervals by the subjects' general practitioner and so is unlikely to be biased by subsequent events. Furthermore, because three quarters of the original cohort was "flagged" on the NHS central registers in England and Scotland and so followed routinely for death, the findings are likely to be representative of the majority of the women originally recruited. Mortality was similar in women

Table 5 Relative risk† of death in users of oral contraceptives compared with never users according to time since last use and duration of use

Cause of death (ICD-8 code)	Current users or last use <10 years previously: All users (95% CI)	Duration of use <10 years (No of deaths)	Duration of use ≥10 years (No of deaths)	Last use ≥10 years previously: All users (95% CI)	Duration of use <10 years (No of deaths)	Duration of use ≥10 years (No of deaths)
All causes (000-999)	1.0 (0.9 to 1.2)	1.0 (254)	1.1 (87)	1.0 (0.9 to 1.1)	1.0 (331)	1.1 (54)
All cancers (140-209)	1.0 (0.8 to 1.2)	0.8 (104)	1.3 (56)	1.0 (0.8 to 1.2)	1.0 (171)	1.2 (32)
Colorectal (153-154)	0.5 (0.2 to 1.2)	0.5 (6)	0.5 (2)	0.6 (0.3 to 1.2)	0.7 (14)	0.0 (0)
Lung (162)	0.9 (0.5 to 1.7)	0.6 (9)	1.6 (10)	1.2 (0.8 to 2.0)	1.1 (27)	2.6 (10)
Breast (174)	1.2 (0.8 to 1.7)	1.1 (40)	1.5 (19)	1.1 (0.8 to 1.5)	1.1 (51)	1.1 (7)
Cervix (180)	2.5 (1.1 to 6.1)*	1.6 (9)	5.3 (8)	1.1 (0.4 to 3.1)	1.2 (6)	1.5 (1)
Ovary (183)	0.2 (0.1 to 0.7)*	0.2 (2)	0.3 (1)	0.7 (0.4 to 1.4)	0.8 (12)	0.0 (0)
Other cancers	0.9 (0.7 to 1.3)	0.9 (38)	1.1 (16)	0.9 (0.7 to 1.3)	0.9 (61)	1.3 (14)
All circulatory diseases(390-458)	1.5 (1.1 to 2.0)**	1.7 (76)	1.1 (16)	1.1 (0.8 to 1.4)	1.1 (85)	1.0 (12)
Ischaemic heart disease (410-414)	1.0 (0.6 to 1.7)	1.2 (21)	0.7 (5)	1.0 (0.7 to 1.5)	1.0 (42)	1.1 (7)
Other heart disease (420-429)	2.8 (0.9 to 8.4)	3.5 (7)	1.3 (1)	0.9 (0.3 to 2.4)	1.0 (7)	0.0 (0)
Cerebrovascular disease (430-438)	1.9 (1.2 to 3.1)*	2.1 (36)	1.5 (8)	1.2 (0.7 to 2.0)	1.2 (26)	1.0 (3)
Other circulatory	1.7 (0.7 to 3.9)	1.8 (12)	1.2 (2)	1.2 (0.5 to 2.7)	1.1 (10)	1.5 (2)
All digestive diseases (520-577)	1.0 (0.5 to 2.2)	0.9 (9)	1.5 (4)	1.1 (0.5 to 2.2)	1.1 (12)	0.7 (1)
Liver disease (570-573)	1.6 (0.6 to 4.4)	1.0 (4)	3.6 (4)	1.7 (0.6 to 4.7)	1.8 (7)	1.9 (1)
All other diseases (1-139, 210-389, 460-519, 578-799)	0.6 (0.4 to 1.0)*	0.7 (25)	0.4 (4)	0.8 (0.6 to 1.2)	0.8 (41)	0.8 (6)
Violent and accidental causes (800-999)	1.3 (0.8 to 2.0)	1.3 (40)	1.4 (7)	1.5 (0.9 to 2.6)	1.5 (22)	1.8 (3)
Suicide (950-959)	1.4 (0.7 to 2.9)	1.4 (19)	1.3 (3)	1.2 (0.5 to 3.1)	1.1 (6)	1.9 (1)

*P<0.05,**P<0.01. †Adjusted for age, parity, social class, and smoking. No significant differences in relative risk were found between women who used oral contraceptives for <10 and ≥10 years.

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who remained under regular follow up by their general practitioner and in women who did not.[3] That overall mortality in our cohort was about 20% below the national average is not unexpected since women with severe chronic illnesses were not recruited.[1 3]

Death certificates were obtained for all women who died. There was good agreement between cause of death recorded on the death certificate and that reported by general practitioners.[5] We adjusted for the potential confounding factors of age, parity, social class, and cigarette smoking. Information on age and parity was updated throughout the follow up, whereas social class and smoking details were recorded at entry only. Information on subsequent smoking habits was obtained in 1994-5 for 11 797 members of the original cohort; re-estimation of the risk of myocardial infarction associated with oral contraceptive use based on the updated data gave virtually identical results to those based on smoking history at entry.[9] Use of information on smoking at entry is thus unlikely to have biased our results. We did not adjust for hypertension or other heart disease because such conditions could be in the causal pathway for death from circulatory diseases. No data on family history of these conditions or of cancer were available, but the absence of such information is unlikely to produce spurious associations suggesting that mortality varies according to the timing of oral contraceptive use.

The specific diseases showing significant excesses or deficits in mortality in our study were generally consistent with the results of other studies on the incidence of these diseases.[1 2 10] Other cohort studies have reported no significant changes in mortality among women who have ever used oral contraceptives, which might at first sight be interpreted as inconsistent with their known effects on incidence of disease.[11 12] What our results highlight, however, is that the effects of oral contraceptives on mortality occur mainly in current and recent users.

The effects of oral contraceptives on circulatory diseases are already recognised to be largely confined to current users, especially if they also smoke.[13–16] There has been concern, however, that oral contraceptive use might affect risk of cancer many years after use stops. The collaborative reanalysis of the worldwide data on the relation between breast cancer and oral contraceptive use, which included data from this study, showed that the incidence of breast cancer was slightly increased while women used oral contraceptives and in the 10 years after stopping use but that there was no excess risk 10 or more years after stopping.[7] Our results are consistent with this finding and suggest that other cancers of the female reproductive organs may also be affected by current and recent use of oral contraceptives but may wear off after use stops. The number of deaths from each type of cancer was small, and further data are needed to confirm our findings. Continued follow up of this and other cohorts will yield important information for the many millions of women throughout the world who have used oral contraceptives.

Key messages

- This 25 year follow up of 46 000 UK women found a decrease in mortality from ovarian cancer and an increase in mortality from circulatory diseases and cervical cancer among women were using oral contraceptives or had used them in the past 10 years
- 10 or more years after stopping use mortality was similar in past users and never users
- Oral contraceptives seem to have their main effect on mortality mainly while they are being used and in the 10 years after stopping use
- There is little evidence to suggest any persistent adverse effect 10 or more years after use of oral contraceptives ceases

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Contributors: CK set up the oral contraception study and PH took over as director in 1994. CH, SD, GR, and VB contributed to the data analysis. VB prepared the first draft of the manuscript and all other authors have contributed to it. CK is guarantor for the quality of the data; VB and CH are guarantors for the analyses and text.

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