Cancers in Australia in 2010 attributable to and prevented by the use of combined oral contraceptives

Susan J. Jordan,[1,2] Louise F. Wilson,[1] Christina M. Nagle,[1,2] Adele C. Green,[1,2,3] Catherine M. Olsen,[1,2] Christopher J. Bain,[1,4] Nirmala Pandeya,[1,2] David C. Whiteman,[1,2] Penelope M. Webb[1,2]

Abstract

Objectives: To estimate the proportion and number of cancers occurring in Australia in 2010 attributable to combined oral contraceptive pill (OCP) use.

Methods: We estimated the population attributable fraction (PAF) for cancers causally associated with combined OCP use (breast, cervix), and the proportion of endometrial and ovarian cancers prevented (prevented fraction [PF]). We used standard formulae incorporating prevalence of combined OCP use in the Australian population, relative risks of cancer associated with this exposure and cancer incidence.

Results: An estimated 105 breast and 52 cervical cancers (0.7% and 6.4% of each cancer, respectively) in Australia in 2010 were attributable to current use of combined OCP. Past combined OCP use was estimated to have prevented 1,032 endometrial and 308 ovarian cancers in 2010, reducing the number of cancers that would otherwise have occurred by 31% and 19%, respectively.

Conclusions: A small proportion of breast and cervical cancers is attributable to combined OCP use; OCP use is likely to have prevented larger numbers of endometrial and ovarian cancers.

Implications: Women seeking contraceptive advice should be told of potential adverse effects, but should also be told that – along with reproductive health benefits – combined OCP use can reduce long-term risks of ovarian and endometrial cancers.

Key words: population attributable fraction, cancer, risk factor, infection

The combined oral contraceptive pill (OCP) was first introduced in Australia in the early 1960s. Although there are many varieties and doses available, all contain an oestrogen and a progestogen. They prevent pregnancy principally by stopping ovulation, although their contraceptive effects are also mediated through changes to cervical mucus and the endometrium.[1] Oestrogens and progestogens in combination can increase or decrease cell proliferation, depending on the target tissue, and it is likely that these effects are responsible for at least some of the observed associations with cancers described below.

The International Agency for Research on Cancer (IARC) in its 2008 review of 20 pharmaceutical agents concluded that there was sufficient evidence that combined oral contraceptives cause cancer of the breast, uterine cervix and liver.[1] They also concluded that use of the combined OCP reduces the risk of endometrial and ovarian cancer. The level of risk associated with each cancer type varies by duration and recency of oral contraceptive use and is summarised in Table 1.

We aimed to estimate the overall number and proportion of cancers diagnosed in 2010 that could be attributed to combined OCP use, as well as the proportion and number of cancers that have – in theory – been prevented by its use. In our primary analysis, we calculated estimates for cancers of the breast and uterine cervix. We did not include liver cancer because it appears that once exposure to the combined OCP has stopped there is no persisting increase in risk.[2] As liver cancer is extremely uncommon in women under the age of 50 in Australia, the number of cases attributable to current combined OCP use would be trivial. We also estimated the numbers and fractions of endometrial and ovarian/fallopian tube cancers (many ovarian cancers may actually arise from the fallopian tube) prevented (avoided) through use of combined OCPs.

Methods

The population attributable fraction of cancers associated with OCP use is the proportion of cancers diagnosed in a given period in a specified population that could potentially have been avoided if no one in the population had used the OCP.[3] We

1. QIMR Berghofer Medical Research Institute, Queensland
2. School of Public Health, The University of Queensland
3. Cancer Research UK, Manchester Institute and Institute of Inflammation and Repair, University of Manchester, United Kingdom
4. National Centre for Epidemiology and Population Health, Research School of Population Health, Australian National University, Australian Capital Territory
Correspondence to: Professor David C. Whiteman, Cancer Control Group, QIMR Berghofer Medical Research Institute, Locked Bag 2000, Royal Brisbane and Women's Hospital, Queensland 4029; e-mail: david.whiteman@qimrberghofer.edu.au
Submitted: March 2015; Revision requested: April 2015; Accepted: May 2015

The authors have stated they have no conflict of interest.

Aust NZ J Public Health. 2015; 39:441-5; doi: 10.1111/1753-6405.12444

Table 1: Summary of of IARC evidence for combined oral contraceptive use and risk of cancer and relative risk estimates and sources.

Cancer Site (ICD-10 codes)	IARC Conclusions		Relative Risk Source and Estimates		
	Level of evidence	Relation between risk and usage patterns	Reference	Study type	Relative Risk
Liver (C22)	Sufficient	Risk occurs in populations at low risk of Hepatitis B (HBV) infection (in HBV endemic populations, risk is assumed to be masked by the large risk associated with HBV infection)	N/A[a]		
Breast (C50)	Sufficient	Risk occurs in young women, among current and recent users only	Collaborative Group on Hormonal Factors in Breast Cancer[4]	Pooled individual data from 54 studies (10 cohort, 44 case-control) conducted in 25 countries. 53,297 women with breast cancer and 100,239 women without breast cancer were included.	Current versus never use: RR = 1.24 (95%CI 1.15–1.33)
Uterine Cervix (C53)	Sufficient	Risk increases with duration of use and declines after cessation of use	International Collaboration of Epidemiological Studies of Cervical Cancer[5]	Reanalysis of individual participant data from 24 studies (9 cohort and 15 case-control) from 26 countries worldwide (about half from less developed countries). 16,573 women with cervical cancer and 35,509 women without cervical cancer were included.	Current versus never use: RR = 1.65 (FSE[b] 0.08)
Endometrium (C54, C55)	Sufficient evidence that cancer risk is reduced	Reduction in risk increases with duration of use and lasts for at least two decades after cessation of use	Dossus et al[7]	EPIC Cohort Study (multicentre prospective cohort study in 10 European countries). Approximately 370,000 female participants. 1,017 endometrial cancer cases diagnosed during an average of 8.7 years of follow-up.	Duration of use (amongst ever users): RR = 0.92 (95%CI 0.90-0.94) per year of use
Ovary (C56)	Sufficient evidence that cancer risk Is reduced	Reduction of risk increases with duration of use and lasts for at least three decades after cessation of use	Collaborative Group on Epidemiological Studies of Ovarian Cancer[6]	Pooled individual data for 23257 women with ovarian cancer, and 87303 women without ovarian cancer from 45 studies (13 cohort, 19 case-control with population controls, and 13 case-control with hospital controls) in 21 countries.	Duration of use (amongst ever users); RR = 0.80 (95%CI 0.77-0.82) per 5 years of use

Source: IARC Working Group on the Evaluation of Carcinogenic Risks to Humans[1]

a: PAFs not calculated for liver cancer; b: FSE= floating standard error

have also calculated the prevented fraction of cancers to estimate of the proportion of cancers that would otherwise have occurred in the absence of any OCP use, but were prevented through prevailing use of the OCP by Australian women.

Relative risk estimates

IARC did not publish any pooled or summary results in its most recent monograph evaluating the carcinogenic risks to humans of pharmaceuticals,[1] so we sourced relative risk estimates for the associations between combined OCPs and the cancers of interest from pooled analyses of individual data (for breast,[4] cervix,[5] and ovarian cancer[6]) and a large, multi-centre prospective cohort study[7] (for endometrial cancer). The latter was the only study to have reported a dose–response relative risk, enabling duration of OCP use to be assessed in our calculations. The estimates of relative risk associated with combined OCP use for all four cancers are summarised in Table 1.

Exposure prevalence estimates

No latent period has been assumed in relation to this exposure. For cervical cancer, risk increases with duration of use and declines after cessation of use. For breast cancer, risk is among current and recent users only. As we did not have access to prevalence data by time since last use of OCPs or duration of use among current users, we modelled the PAF using relative risks for current versus never use, restricting our analyses to women under 50 years of age, as OCP use would be rare above this age. For endometrial and ovarian cancer, the protective effects increase with duration of use among ever-users and the effects appear to persist for at least two decades after stopping use,[1] so we modelled the effects of total duration of use regardless of whether this was current or past.

The most recent nationally representative data regarding current use of OCPs come from the 2001 National Health Survey Confidentialised Unit Record Files.[8] Women aged 18–49 years were asked whether they had ever used the contraceptive pill, if they were currently using the contraceptive pill, and the age that they had first started using the pill.[9] We used these data and assumed that the proportion of women (aged 18–49 years) currently using oral contraceptives remained stable over the ensuing decade to 2010. The 2005 Household, Income and Labour Dynamics Australia (HILDA) survey of women aged 18–44 years reported very similar prevalence figures,[10] lending support to our assumption of stability of use. We did not use the more recent HILDA estimates, as this survey had a smaller sample and narrower age group coverage than the 2001 NHS. We also assumed that a negligible number of women aged over 49 years would be currently using OCPs, and did not include these women in our calculations. Furthermore, we assumed that all women used combined OCPs, given that the vast majority (90%) of prescriptions for oral contraceptives in 2010[11] were for combined pills, and because it is much less common for women to use progestogen-only contraceptives for long periods of time.

The only contemporary Australian population-based prevalence data for duration of use of OCPs that we could obtain were from 1,502 women who participated as controls in the Australian Ovarian Cancer Study (AOCS). These women were aged 18–79 years when recruited between 2003 and 2006. They were randomly selected from the national electoral roll and frequency matched by age (in 5-year age bands) and state of residence to the case group. Of eligible women contacted, 47% returned a completed questionnaire.[12]

Statistical analysis

For breast and cervical cancer, the relative risks were for current versus never use of combined OCPs. For these cancers, the PAF was calculated using the following formula:[3]

$$\mathrm{PAF} = \frac{\Sigma(p_x \text{ x } \mathrm{ERR}_x)}{1 + \Sigma(p_x \text{ x } \mathrm{ERR}_x)}$$

where p_x is the proportion of Australian women currently using oral contraceptives in each age category x, and ERR_x is the excess relative risk (RR_x -1) for current use (for each of the respective cancers).

To obtain the number of cancers attributable to combined OCP use, the PAF was multiplied by the number of incident cancers at that site in 2010[13] for each age category (using the latest incidence data available from the Australian Institute of Health and Welfare).

For endometrial and ovarian cancers, we calculated the Prevented Fraction (PF) using the following formula:[3]

$$PF = \sum P_y(1 - RR_y)$$

where P_y is the proportion of the population in each age and 'duration of use' category y and RR_y is the relative risk for each 'duration of use' category y compared to never users.

We calculated RR_y using the formula:

$$RR_y = exp((\ln(RR)/X) * Duration\ Category\ Midpoint)$$

where RR is the relative risk of endometrial or ovarian cancer per X years of OCP use.

To estimate the number of cancers that would have occurred, but were prevented through use of combined OCPs, the following formula was used:

$$Est.number\ of\ cancers\ prevented = \Sigma\left(\frac{N_x}{1 - PF_x}\right) - N_x$$

where N_x is the observed number of cancers in 2010 in each age category and PF_x is the prevented fraction in each age category.

The sum of the estimated numbers of cancers prevented across each age category is then expressed as a percentage of the total number of cancers expected in the absence of any protection (i.e. number observed + number prevented).

Results

More than one-quarter of all women aged 18 to 49 years surveyed in the 2001 NHS were currently taking the OCP. This proportion was highest (about 41%) in women aged under 30 years, declining steadily to 8% in women aged 45–49 years (Table 2).

In the AOCS control group, 25% of women had never used OCPs. This proportion varied by age, ranging from 6.9% in the 40–44 year age group to 63% in women aged over 70 years. More than 20% of all women had used oral contraceptives for between 10 and 20 years; 5.5% had used OCPs for more than 20 years (Table 2).

We estimated that 157 cancers (105 breast and 52 cervical) in Australian women younger than 50 years of age could be attributed to current use of combined OCPs in 2010 (0.7% and 6.4% of all breast and cervical cancers, respectively, and 3.2% and 12.3% of those in women aged under 50 years). This was 0.3% of all cancers (excluding basal cell carcinoma and squamous cell carcinoma of the skin) diagnosed in women in 2010 and 1.7% of all cancers diagnosed in women aged under 50 years (Table 3).

In contrast, an estimated 31% of endometrial cancers and 19% of ovarian cancers that would otherwise have occurred in 2010 were prevented through combined OCP use (Table 3). This suggests that, in the absence of the combined OCP, an additional 1,032 endometrial cancers and 308 ovarian cancers would have been diagnosed in 2010.

Discussion

In our primary analysis, we estimated that 157 cancer cases (105 breast and 52 cervical) in women younger than 50 years in 2010 could be attributed to their current use of combined OCPs; 0.7% and 6.4% of all breast and cervical cancers, respectively. In contrast, combined OCP use was estimated to have prevented 1,340 cancers (1,032 endometrial and 308 ovarian) in 2010, reducing the number of endometrial and ovarian cancers that would otherwise have occurred if women did not use combined OCPs by 31% and 19% respectively.

PAFs associated with the combined OCP have been previously published for the UK[14] and France.[15] The estimates for breast cancer were slightly higher for these countries (1.1% and 1.0%, respectively) probably reflecting different prevalence of oral contraceptive use (for example, 40% of Australian women aged 25–29 years were currently using oral contraceptives in 2001, compared to 54% of French women in the same year[15]). Estimates for the other cancers were not reported in the French study, but for the UK study the PAF for cervical cancer was slightly higher at 9.7% and for ovarian and endometrial cancer the UK estimates were somewhat lower (16.9% and 9.3% respectively).[14] The UK PAF project had prevalence data on current use, past use and time since last use of oral contraceptives,[14] so the difference may reflect the ways in which prevalence data were applied. It is also possible that there are differences in patterns of duration of use between the populations; however, comparable data are not available for us to assess this.

The exact mechanisms whereby the combined OCP contributes to carcinogenesis is not completely clear, but there are several possibilities. Oestrogens and progestogens induce breast cell proliferation, particularly when both hormones are present.[16] In general, the breasts of women taking the combined OCP are exposed to the combined proliferative effects of oestrogen and progestogens for longer per cycle than those not taking the OCP, possibly increasing the risk of DNA damage and neoplastic transformation. The cumulative

Table 2: Proportion (%) of current oral contraceptive users (National Health Survey 2001) and duration of use among ever users (AOCS controls).

Duration of use	Age groups (years)											
	<25	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70+	Total
Current use[a]	43.2	40.4	29.4	22.2	14.5	7.9	-	-	-	-	-	26.9
Duration of use[b]												
Never	33.3	12.5	11.6	10.1	6.9	12.9	11.4	15.5	25.5	37.2	63.1	24.8
1-5 yrs	66.7	41.7	25.6	21.7	21.6	22.1	30.5	32.6	25.5	28.7	15.1	26.0
6-10 yrs	0.0	33.3	30.2	14.5	25.0	26.4	24.3	26.4	22.9	17.1	10.7	21.4
11-15 yrs	0.0	12.5	25.6	30.4	19.0	13.5	14.3	14.6	14.3	8.5	6.7	13.7
16-20 yrs	0.0	0.0	7.0	23.2	23.3	11.0	9.5	7.5	4.3	4.9	3.6	8.5
21-25 yrs	0.0	0.0	0.0	0.0	4.3	9.8	6.7	1.3	4.8	2.4	0.9	3.7
26-30 yrs	0.0	0.0	0.0	0.0	0.0	4.3	3.3	2.1	1.7	0.6	0.0	1.6
>30 yrs	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.9	0.6	0.0	0.2

a: 2001 National Health Survey, Australian Bureau of Statistics[8]

b: Australian Ovarian Cancer Study Controls[12]

Table 3: Population attributable fractions (PAF) and estimated numbers of cancers diagnosed in Australia in 2010 attributable to use of combined oral contraceptives and estimated numbers of endometrial and ovarian cancers prevented in 2010 due to use of combined oral contraceptives.

	Estimated Cancers Caused								Estimated Cancers Prevented						
Age Group	Breast Cancer (C50)[a]			Cervical Cancer (C53)[a]			All Cancers[b]			Endometrial (C54, C55)[a]			Ovarian Cancer (C56)[a]		
	PAF	Obs.	Exc.	PAF	Obs.	Exc.	Obs.	Exc.		PF	Obs.	Prev.	PF	Obs.	Prev.
<25 yrs	9.4	7	1	21.9	20	4	647	5		12.5	1	0	7.0	25	2
25-29 yrs	8.8	67	6	20.8	56	12	568	18		31.4	7	3	19.2	14	3
30-34 yrs	6.6	191	13	16.0	75	12	833	25		40.8	12	8	26.0	24	9
35-39 yrs	5.1	502	25	12.6	104	13	1494	38		48.3	41	38	32.0	30	14
40-44 yrs	3.4	918	31	8.6	74	6	2142	37		49.5	62	61	32.8	47	23
45-49 yrs	1.9	1,563	29	4.9	97	5	3416	34		45.8	122	103	30.8	89	40
50-54 yrs	0.0	1,822	0	0.0	71	0	4396	0		42.2	240	176	28.0	108	42
55-59 yrs	0.0	1,837	0	0.0	75	0	5038	0		36.6	352	203	23.6	138	42
60-64 yrs	0.0	2,056	0	0.0	59	0	6004	0		34.5	369	194	22.6	146	43
65-69 yrs	0.0	1,734	0	0.0	52	0	5859	0		25.8	319	111	16.6	165	33
70+ yrs	0.0	3,483	0	0.0	135	0	20199	0		15.6	731	135	10.0	518	57
Total		14,180	105		818	52	50598	157			2,256	1,032		1,304	308
PAF_{aw}	3.2[c]			12.3[e]			PAF_{aw} =	1.7[g]	PF_{aw}	31.4			19.1		
	0.7[d]			6.4[f]			PAF_{aw} =	0.3[h]							

Abbreviations: Obs. = observed cancers in 2010; Exc. = excess cancers in 2010 attributable to combined OCP use; Prev. = cancers prevented in 2010 through use of combined OCP; PAF = population attributable fraction (expressed as a percentage); PAFaw = age-weighted population attributable fraction (expressed as a percentage); PF = prevented fraction (expressed as a percentage); PFaw = age-weighted prevented fraction (expressed as a percentage)

a: International Classification of Diseases Code (ICD-10)

b: excluding basal cell carcinoma and squamous cell carcinoma of the skin

c: % of breast cancers in women 0-49 years

d: % of all breast cancers

e: % of cervical cancers in women 0-49 years

f: % of all cervical cancers

g: % of all cancers (excluding basal cell carcinoma and squamous cell carcinoma of the skin) in women 0-49 years

h: % of all cancers (excluding basal cell carcinoma and squamous cell carcinoma of the skin)

greater exposure to combined oestrogen and progestogen may also be important for cervical cancer. Cervical cancer is caused by human papillomavirus but, among women with the virus, oestrogens and progestogens may enhance expression of some HPV genes and may promote cervical cell proliferation, increasing the likelihood of neoplastic transformation.[2]

Several processes may contribute to the protective effect of combined OCPs on ovarian/fallopian tube cancer.[2] This may be through direct hormonal effects such as reductions in gonadotrophins[17] and androgens[18] or the apoptotic effects of potent synthetic progestogens;[18] or through suppression of the physical effects of ovulation itself,[19] with concomitant reductions in exposure of the ovarian/fallopian tube epithelium to inflammatory or hormonal factors that could result in neoplastic changes. The combined OCP also reduces retrograde menstruation, which has also been implicated in ovarian carcinogenesis.

The chemoprotective effects of oral contraceptives on endometrial cancer probably result from the effects of the progestogen component of combined OCPs. Although oestrogens stimulate proliferation of endometrial cells, they do this only in the absence of a progestogen. Progestogens induce terminal differentiation in endometrial cells so that they no longer proliferate and the risk of neoplastic transformation is reduced.[2,16]

The major limitation of our analyses was the lack of contemporary comprehensive prevalence data for OCP use in Australia. Our data for current use were sourced from the 2001 National Health Survey and, although those data should represent the true population prevalence in 2001, we had to assume that there had been no major changes in usage patterns between 2001 and 2010. While this is probably a reasonable assumption, alternative contraceptive methods such as progestogen-releasing implants and intrauterine devices have become available in Australia in the last 10–15 years, and usage of these may be increasing and displacing the combined OCP.[20] If use of OCPs has decreased since 2005, then a proportional decrease in the number of breast and cervical cancers caused by current use may be expected. A more limited effect on the number of endometrial or ovarian cancer cases in 2010 would be expected, because most of these cancers would have occurred among post-menopausal women who would have stopped using the OCP several years earlier. Any effects of recent changes on endometrial and ovarian cancers will therefore only be seen in the future. There are also insufficient data available on how the contraceptive options that may have replaced the OCP (long-acting progesterone-releasing implants and intrauterine devices) influence cancer risk, so the net effect of such usage changes are difficult to gauge.

Perhaps more uncertain is the reliability of the data we used for duration of OCP use, which was necessary to estimate the prevented fractions of ovarian and endometrial cancer. The only contemporary Australian source of these data was the population-based control group recruited between 2003 and 2006 for the Australian Ovarian Cancer Study. The participation proportion among potential controls was about 50% and, as the proportion of ever-users was higher in the AOCS control women than in the NHS, it is possible that our estimates for duration of use were also higher than the general population. Thus, we may have overestimated the prevented fractions for endometrial and ovarian cancer. We were also unable to assess the effects of time since stopping the OCP and we therefore assumed that risk of breast and cervical cancer returns to normal

immediately after stopping. This assumption may have biased our estimates for these cancers downwards.

Another limitation relates to information on types of OCPs. IARC's conclusions for the carcinogenic (or protective) effects apply only to combined oestrogen-progestogen oral contraceptives; whether progestogen-only oral contraceptives influence cancer risk is much less clear. There are no Australian prevalence data on contraceptive use by type. However, data from the Australian Statistics on Medicines (2010) indicate that about 90% of prescriptions for contraceptives in 2010 were for combined preparations.[11] Moreover, long-term use of oral progestogens is uncommon, so the effect on our estimates is likely to have been small.

Overall, our analyses suggest that the use of combined OCPs confers far more benefit than harm with respect to cancer incidence, with a modest increase in the number of breast/cervical cancer cases weighed against a much larger decrease in numbers of endometrial and ovarian cancers. However, along with small increases in cancer, the combined OCP can have other adverse effects such as thromboembolic disease, so its broad use as a cancer chemopreventive agent cannot be promoted. Women seeking contraceptive advice should be advised not only of the potential adverse effects but also that, along with its benefits to reproductive health, use of the combined OCP can reduce their long-term risk of ovarian and uterine cancers.

Acknowledgements

This work was supported by a grant from Cancer Council Australia. SJJ, NP, DCW, and PMW were supported by Research Fellowships from the National Health and Medical Research Council of Australia (NHMRC). CMO, CMN, and CJB were supported by a NHMRC Program Grant (552429). The funding bodies had no role in the design and conduct of the study, the collection, management, analysis, and interpretation of the data, or the preparation, review, or approval of the manuscript.

SJJ and LFW contributed equally to this manuscript and share first authorship.

PAF Project

Chief Investigators: David C. Whiteman, Penelope M. Webb, Adele C. Green, Rachel E. Neale, Lin Fritschi

Associate Investigators: Louise F. Wilson, Catherine M. Olsen, Christina M. Nagle , Nirmala Pandeya, Susan J. Jordan, Annika Antonsson, Bradley J. Kendall, Torukiri I. Ibiebele, Maria Celia B. Hughes, Kyoko Miura, Susan Peters, Renee N. Carey

Advisers: Christopher J. Bain, D. Max Parkin

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