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Cancers attributable to exposure to hormones in the UK in 2010

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The International Agency for Research on Cancer (IARC) Monographs on the carcinogenic risk to humans concluded that combined oral oestrogen – progestogen contraceptives are carcinogenic to humans (IARC, 2007). This evaluation was made on the basis of increased risks for cancer of the breast (among current and recent users only), cervix and liver (in populations that are at low risk for hepatitis B viral infection). There is also convincing evidence in humans that these agents confer a protective effect against cancer of the endometrium and ovary.

The IARC (2007) review also concluded that there is sufficient evidence in humans for the carcinogenicity of combined oestrogen – progestogen menopausal therapy in the breast. With respect to endometrial cancer, combined oestrogen – progestogen menopausal therapy was evaluated as carcinogenic when progestogens are taken for <10 days per month, while there was evidence suggesting lack of carcinogenicity in the endometrium when progestogens are taken daily. The risk for endometrial cancer is inversely associated with the number of days per month that progestogens are added to the regimen.

The use of hormonal preparations in the UK has declined dramatically in recent years. According to the data from prescription cost analysis (PCA) on the annual numbers of prescriptions for oestrogens and progestogens dispensed in the community, there has been a marked decline in prescriptions for hormonal preparations in England since 2000 – 1 (http://www.ic.nhs.uk/statistics-and-data-collections/primary-care/prescriptions/prescription-cost-analysis-england–2009).

In this section, the population-attributable fraction (PAF) of cancers diagnosed in women in the UK in 2010 due to current or past use of hormonal preparations is estimated.

METHODS

Prevalence of exposure to hormonal preparations

To examine the changes in use of prescribed agents by age group, data were obtained from the general practice research database (GPRD). The GPRD is the world's largest computerised database of anonymised longitudinal medical records from primary care. Currently data are collected on over 3.4 million active patients from around 450 primary-care practices throughout the UK. Data were abstracted for women, aged 15 to >85 (in 5-year age bands), annually from 1992 to 2009. A list of female sex hormone products were identified and classed into one of the following British National Formulary (BNF) categories:

6.4.1.0 – Oestrogen only hormone replacement therapy (HRT)
6.4.1.1 – Combined oestrogen/progesterone HRT
6.4.1.2 – Progestogens
6.4.1.3 – Tibolone
6.4.1.4 – Raloxifene
7.3.1 – Combined hormonal contraceptives
7.3.2.1 – Oral progestogen-only contraceptives
7.3.2.2 – Parenteral progestogen-only contraceptives
7.3.2.3 – Intra-uterine progestogen-only device
Other – Other female sex hormones.

The information was provided by GPRD as prevalence of women with a prescription per 1000 patients registered at calendar year mid-point, stratified by calendar year, age band and BNF code. As well as prevalence of current (2009) use, the prevalence of ex-users in the same year was estimated, with the simplifying assumption that users do not stop and restart the same preparation. Thus, the prevalence of ex-users of <1 year (Pex(1)) is given by

$$\mathrm{Pex}(1)_{i,a} = [P\mathrm{current}_{i-1,a-1}] - [P\mathrm{current}_{i,a}]$$

where i is the year and a age.

In addition, it was assumed that prescription of progesterone-only preparations in post-menopausal women was accompanied by oestrogens (with each hormone dispensed separately, rather than as a combined preparation), so that prevalence of use of unopposed oestrogens (P(oes)) is given by the difference (P(oes)$-P$(prog)).

Risks of oral contraceptive (OC) use

Breast cancer The Collaborative Group on Hormonal Factors in Breast Cancer (1996) brought together and reanalysed the worldwide epidemiological evidence on the relation between breast cancer risk and use of hormonal contraceptives. Table 1 shows the excess relative risks (ERRs) ($=$relative risk (RR)-1) associated with current and past use of combined (oestrogen plus progesterone) OC preparations. Duration of use, age at first use, and the dose and type of hormone within the contraceptives had little additional effect on breast cancer risk, once recency of use had been taken into account. Hormonal contraceptives containing only progestogens comprised $<3\%$ of the study population, but results

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were broadly similar to those found for combined OCs (an increase in risk for use in the previous 5 years: ERR 0.17; but no evidence of an increase in risk 10 or more years after stopping use); risks are assumed to be the same as for combined contraceptive preparations (Table 1).

Cancer of the cervix uteri Smith *et al* (2003) combined the results from studies published between 1966 and 2002 to examine the relationship between the risk of cancers of the cervix and duration and recency of use of hormonal contraceptives, taking into account potential confounding factors, such as HPV status, sexual partners, screening history, smoking and use of barrier contraceptives. More recently, the International Collaboration of Epidemiological Studies of Cervical Cancer (2007) obtained the original data from 24 studies to conduct a pooled analysis. They found that risk of cervical cancer increased by a factor of 1.07 for each year of use of hormonal contraception (or 1.38 (1.30–1.46) for 5 years use). In ex-users, the excess risk is approximately halved 2–4 years after cessation, and halved again after 5–9 years. There was no significant excess risk 10 years after cessation of use.

Duration of use of contraception, among current users, by age group, is not available from any UK source. In the multicentre study of the International Collaboration (2007), the mean duration of use, in control women, was 6 years. Clearly, the controls for cases of cervix cancer are older women, with a mean age of about 40. Younger women would have had shorter durations of use: we assume 2 years at ages 15–19 and 4 years at ages 20–24, so that the ERRs of current users are as shown in Table 2. For ex-users, we assume a halving of risk after 2–4 years, and halving again at 5–9, as in the International Collaboration Study (2007).

Cancer of the corpus uteri (endometrium) IARC (2007) concluded that there is convincing evidence in humans for a protective effect of combined oral oestrogen–progestogen contraceptives against carcinogenicity in the endometrium. They reviewed four cohort studies and 21 case–control studies reported up to 2003, which consistently showed that the risk for endometrial cancer in women who had taken these medications is approximately halved. The reduction in risk was generally greater with longer duration of use of combined hormonal contraceptives and persisted for at least 15 years after cessation of use. More recently, the EPIC study (Dossus *et al*, 2010) found that women who had ever used OCs had a risk of 0.63 compared with never users, and this was just 0.44 in women who had used OCs for $\geqslant 10$ years.

Schlesselman (1997) conducted a meta-analysis of studies reported up to 1993, and estimated the risk of combined OC use in relation to duration of use, and time since last used. The estimate of RR by duration of use was given by

$$RR_{dur} = \exp\left[-0.023 - 0.493 \times \ln(\text{years} + 1)\right]$$

This is equivalent to a risk of 0.44 for 4 years use, 0.33 for 8 years use and 0.28 for 12 years use.

The estimate of RR by years since last use of combined OCs (recency of use) was given by

$$RR_{rec} = \exp\left[-1.721 + 0.346 \times \ln(\text{years} + 1)\right]$$

This is equivalent to a risk of 0.33 for use within the last 10 years, 0.41 for use within the last 10 years and 0.51 for use within the last 20 years.

Ovarian cancer The IARC (2007) review concluded that women who had ever used combined hormonal contraceptives orally had an overall reduced risk for ovarian cancer, and an inverse relationship was observed with duration of use. The reduced risk appeared to persist for at least 20 years after cessation of use. In the combined analysis by the Collaborative Group on Epidemiological Studies of Ovarian Cancer (Collaborative Group, 2008), the overall reduction in ovarian cancer risk in ever *vs* never users was 27%. Table 3 shows the RRs by duration of use and time since last use.

The effect of combined hormonal contraceptive use on the reduction of risk for ovarian cancer is not confined to any particular type of oral formulation nor to any histological type of ovarian cancer, although it was less consistent for mucinous than for other types in several studies.

Liver cancer Although the IARC (2007) review concluded that combined oral oestrogen–progestogen contraceptives are carcinogenic for the liver, the conclusion was based on a selected group of case–control studies (in populations with 'low prevalence of hepatitis B viral infection and chronic liver disease'), with no cohort studies providing a conclusive result. A more recent meta-analysis of case–control studies (Maheshwari *et al*, 2007) did not obtain a conclusive result based on 12 case–control studies (pooled estimate of ORs 1.57 (95% CI = 0.96–2.54, $P = 0.07$)), or eight studies reporting adjusted ORs (in addition to age and sex) – the pooled estimate was 1.45 (95% CI = 0.93–2.27, $P = 0.11$).

In any case, liver cancer is rare in UK, and there were only some 190 cases below age 50 in UK in 2005; therefore, the number of cases possibly attributable to OC use is trivial.

Table 1 Excess relative risk of breast cancer associated with current and past use of combined OC preparations

Time since cessation of OCs (years)	Excess relative risk of breast cancer
Current use	0.24
1–4	0.16
5–9	0.07
$\geqslant 10$	0

Abbreviation: OC = oral contraceptive.

Table 2 Excess relative risks for cervical cancer in relation to use of OCs, by age

Time since cessation of OCs (years)	Excess relative risk by age group		
	15–19	20–24	25+
Current use	0.14	0.30	0.48
<1	0.14	0.30	0.48
2–4	0.07	0.15	0.24
5–9	—	0.07	0.12
$\geqslant 10$	—	—	0

Abbreviation: OC = oral contraceptive.

Table 3 Risk of ovarian cancer in relation to duration of use, and time since last use of OCs (Collaborative Group, 2008)

Time since use of OCs (years)	Risk of ovarian cancer by duration of use of OCs		
	<5 years	5–9 years	>10 years
<10	0.88	0.52	0.39
10–19	0.85	0.62	0.51
29–29	0.81	0.69	0.60
$\geqslant 30$	0.83	—	—

Abbreviations: OC = oral contraceptive.

Risks of post-menopausal hormone therapy

Breast cancer The magnitude of the risk of postmenopausal hormone therapy for the risk of breast cancer has been quantified based on studies in the USA, Europe and the UK (Collaborative Group, 1997; Writing Group, 2002; Chlebowski *et al*, 2003; Beral, 2003; Bakken *et al*, 2011). In the Million Women Study (Beral, 2003) for example, the RR of breast cancer in current users of HRT was 1.66 (95% CI 1.58–1.75, $P<0.0001$). Incidence was significantly increased for current users of preparations containing oestrogen only (1.30), progestogen only (2.02), oestrogen–progestogen (2.00) and tibolone (1.45). Results varied little between specific oestrogens and progestogens or their doses, or between continuous and sequential regimens. Past users of HRT were, however, not at an increased risk of disease (1.01 (0.94–1.09)). In past users, the risk of breast cancer did not differ significantly from that of never users of HRT, for use that ceased at <5 years, 5–9 years and $\geqslant 10$ years previously, although among women who ceased use of HRT in the previous year, the RR of breast cancer was slightly increased (1.14 (1.01–1.28)). The ERRs are shown in Table 4.

Cancer of the corpus uteri (endometrium) The Million Women Study (Beral *et al*, 2005) found that hormone-replacement therapy containing oestrogen alone increased the risk of endometrial cancer. The RR of endometrial cancer in current users of oestrogen-only HRT was 1.80 (1.19–2.70), while there was no increase in risk in past users (RR 0.97 (0.50–1.87)).

The risk of endometrial cancer was also increased by tibolone. The RR in current users of tibolone was 2.02 (1.58–2.59), while it was 1.23 (0.76–1.99) in past users. Past users had ceased use an average of 2.7 years previously, so that the excess risk in past users of tibolone (0.23) was assumed to last for up to 4 years.

Progestogens, however, counteract the adverse effect of oestrogens on the endometrium, and the effect of continuous combined preparations was a reduction in risk (RR = 0.71), while there was no significant risk (or protection) from use of cyclic preparations (RR = 1.05, 95% CI 0.91–1.22). As the data from GPRD did not distinguish between the proportion of combined oestrogen–progestogen preparations that had been prescribed as continuous combined preparations, or cyclic combined preparations, it was assumed that these were in the ratio of 1:2, as in the Million Women study. An RR for all such preparations was obtained by weighting the RRs of current use (0.75 for continuous, 1.05 for cyclic) accordingly, yielding an RR of 0.95 and an ERR of −0.05 (Table 6). There were no significant differences in risk between current and past users of combined preparations (average time since cessation for women who had taken cyclic preparations was 2.7 years, and that for continuous 1.2 years).

The ERRs used to estimate PAF are shown in Table 5.

Table 4 Excess relative risks of breast cancer in current and past users of HRT

	Excess relative risk of breast cancer	
Preparation	**Current HRT users**	**Past HRT users (<1 year)**
Oestrogen only	0.3	0.06
Oestrogen+progestogen combinations	1	0.21
Progestogens	1.02	0.22
Tibolone	0.45	0.10
Raloxifene hydrochloride	0	0.00
All	0.66	0.14

Abbreviation: HRT = hormone replacement therapy (postmenopausal hormones).

Ovarian cancer The IARC (2007) review concluded that the studies available were inadequate to evaluate an association between ovarian cancer and combined oestrogen–progestogen hormonal therapy. However, more data are now available. In a meta-analysis of eight cohort and 19 case–control studies by Zhou *et al* (2008), ever use of HRT was associated with a 19–24% increase in risk of ovarian cancer, with a greater risk of oestrogen-only therapy compared to oestrogen–progestogen therapy. A more recent meta-analysis of 14 population-based studies found a risk of 1.22 associated with 5 years of use of oestrogen therapy, while in users of combined therapy it was 1.1 (Pearce *et al*, 2009). In the Cancer Prevention II Nutrition Cohort in the USA (Hildebrand *et al*, 2010), current oestrogen use was associated with a risk of 1.70 (for use of $\leqslant 10$ years), while there was no increased risk for users of combined preparations, or in former users of either.

After an average 5.3 years of follow-up in the Million Women Study (Million Women Study Collaborators, 2007), the risk in current users of HRT was 1.20, greater for oestrogen-only (1.34) than for combined (1.14) or other preparations (1.22). The risk in past users was not increased. These values were used to estimate PAF in the UK in 2010.

Attributable fractions

Breast cancer We use the prevalence of current and past use of OC agents, and post-menopausal therapy in 2009 to calculate the excess risk in current users, given the ERRs in Tables 1 and 4. It was assumed that prescription of progestogen-only preparations in post-menopausal women was probably accompanied by oestrogens (with each hormone dispensed separately, rather than as a combined preparation). Total excess risk due to hormonal preparations is obtained by summing the excess risks for current and past users of HRT and OCs.

Cervix cancer With the ERRs in Table 2 and prevalence of current and past use of OCs, total excess risk due to OCs is obtained by summing the excess risks for current and past users (as for breast cancer, above).

Endometrial cancer The protective effect of combined OCs against endometrial cancer is related to duration of use, and, in ex-users, time since last use, as described above. The prevalence of current and past use of OCs in the UK (by age, time since used and duration of use) is not documented. We used data from the Million Women Study (age groups 50–64) (Million Women Study Collaborative Group, 1999), from a study of post-menopausal women in Norfolk (Chan *et al*, 2008), and from a case–control study of pre-menopausal women (aged 36–44) by Roddam *et al* (2007) to estimate the proportions of current and past users of OCs. Prevalence of current and recent (<10 years) ex-users at ages 15–34 was estimated from the GPRD data as described above. With these data, and the equations proposed by Schlesselman (1997), estimates of RR by age, duration of use and time since last use could be made for 2009. These were applied to the estimated

Table 5 Excess relative risks of endometrial cancer in current and past users of HRT

	Excess relative risks of endometrial cancer	
Preparation	**Current HRT users**	**Past HRT users (used HRT within the past 4 years)**
Oestrogen only	0.8	0.00
Oestrogens+progestogen combinations	−0.05	−0.05
Tibolone	1.02	0.23

Abbreviation: HRT = hormone replacement therapy.

numbers of cancers in 2010 to estimate the proportion being prevented by current and past use of combined OCs.

For post-menopausal hormone therapy, the prevalence of use at ages $\geqslant$45 in 2009 was used to calculate the excess risk of endometrial cancer in current users of oestrogen-only preparations, and of tibolone, with an ERR for oestrogen of 0.80 and for tibolone of 1.02 (Table 5). As noted earlier, it was assumed that progestogen-only preparations in post-menopausal women were accompanied by oestrogens (with each hormone dispensed separately, rather than as a combined preparation), so that prevalence of use of oestrogen alone is represented by the difference (oestrogen−progestogen).

Ovarian cancer The prevalence of current and past use of OCs in the UK (by age, time since used and duration of use) was estimated as described for endometrial cancer. With the relevant protective effects from the Collaborative Group study (2008) shown in Table 3, the proportion of cancers being *prevented* by current and past use of OCs in 2010 can be estimated.

For use of post-menopausal hormone therapy, we used the prevalence of use of post-menopausal therapy (ages 45 and over) in 2009 to calculate the excess risk of ovarian cancer in current users of the different preparations, assuming the RRs from the Million Women Study (Million Women Study Collaborators, 2007): oestrogen-only HRT: 1.34, combined preparations: 1.14, others: 1.22 (as usual, also assuming that prescription of progestogen-only preparations in postmenopausal women was accompanied by oestrogens).

RESULTS

Prevalence of exposure to hormonal preparations

Prevalence of use of female sex hormones is greatest in the age group 20–24, when almost 60% of women were receiving a prescription for such agents (Figure 1).

Prescribed hormones in the UK were predominantly combined oestrogen–progesterone OCs, with a smaller proportion of progestogen-only contraceptives, increasing over time. Prevalence of use of contraceptive agents declines with age. The estimated age-specific prevalence, based on prescription data, is very similar to that from the 'Omnibus survey' of 2006–7 (Lader, 2007), reporting prevalence of use of OCs in England as 64% at ages 20–24 and 28% at 35–39. Use of hormonal (non-contraceptive) agents exceeds use of contraceptive agents by age 45–49, and increases to a maximum prevalence in the age group 50–54.

There have been marked changes in use over time. Use of hormonal preparations increased for several years from 1992 to reach a maximum in around 2000, and then declined. The year of maximum use (in terms of women receiving prescriptions) varies with age, from 1997 (ages 45–49), to 2001 (55–59) and 2002 (65–69). Figure 2 shows the prevalence of use of different hormonal agents in women aged 45–69. The changes concern in particular combined oestrogen–progesterone preparations, but use of oestrogen-only agents has also declined.

Attributable fractions

Table 6 summarises the estimates of PAF due to use of OCs and post-menopausal hormone therapy, and the net result of both, on the estimated numbers of cases of breast, cervical, endometrial and ovarian cancers in 2010.

Breast cancer Both post-menopausal hormone therapy and OCs increase the risk of breast cancer. Post-menopausal hormones are estimated to be responsible for 3.2% of breast cancers in 2010, and OCs for 1.1%, so that both sources of hormones together are responsible for 4.3% of breast cancers. Figure 3 shows the estimated fractions that are attributable to hormones, by age group. The excess risk of breast cancer was highest (a 14% excess) in the age ranges with maximum use of contraceptives (20–24) so that the fraction of breast cancer cases attributable to hormones was about 12%.

Cervix cancer The fraction of cervix cancer cases attributable to OCs is 9.7%, with much larger proportions (up to 22%) in younger women (Figure 4).

Endometrial cancer It is estimated that current and past use of OCs is preventing almost 17% of cases of endometrial cancers that would otherwise have occurred.

Because the bulk of post-menopausal hormones are prescribed as combined oestrogen–progestogen preparations, with a small net protective effect (assuming that two-thirds of them are given as continuous combined preparations), the net effect on the risk of endometrial cancer is small. The estimate of the fraction of endometrial cancers attributable to use of post-menopausal

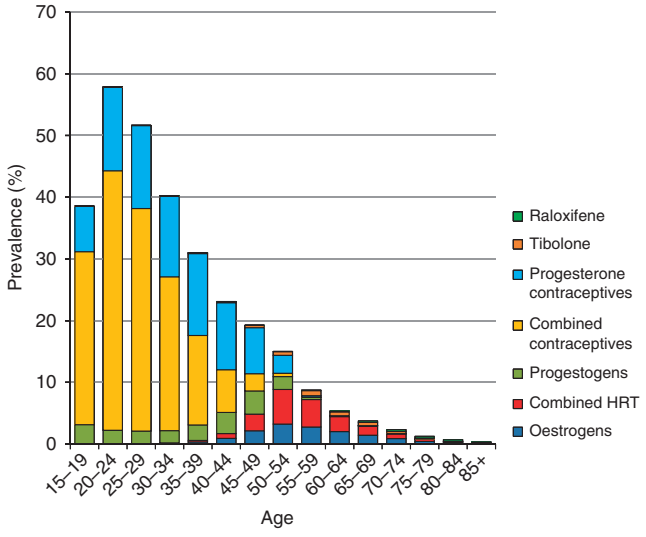

Figure 1 Prevalence (%) of women prescribed hormones, UK 2009.

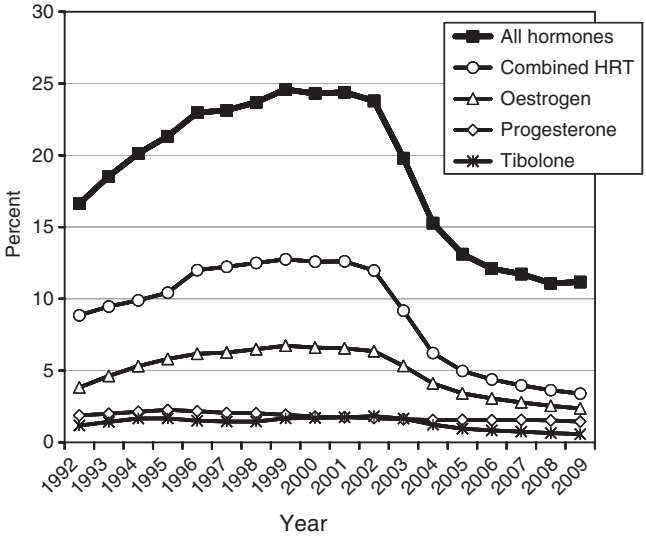

Figure 2 Women aged 45–69 prescribed hormonal agents, 1992–2009.

Table 6 Estimated cases of cancers of the breast, cervix, endometrium and ovary occurring in 2010 attributable to exposure to hormones

		Cases attributable to exposure to hormones, by hormone type					
		HRT		Oral contraceptives		Both	
Cancer and age (years)	Observed cases	Excess attributable cases	PAF (%)	Excess attributable cases	PAF (%)	Excess attributable cases	PAF (%)
Breast							
<40	2018	0	0.0	192	9.5	192	9.5
40–49	6829	376	5.5	343	5.0	719	10.5
50–64	16851	921	5.5	0	0.0	921	5.5
⩾65	22687	235	1.0	0	0.0	235	1.0
All ages	48385	1531	3.2	535	1.1	2067	4.3
Cervix							
<40	1108	0	0.0	203	18.3	203	18.3
40–49	544	0	0.0	54	10.0	54	10.0
50–64	494	0	0.0	4	0.8	0	0.0
⩾65	547	0	0.0	0	0.0	0	0.0
All ages	2691	0	0.0	261	9.7	261	9.7
Corpus uteri (endometrium)							
<40	104	0	0.0	−74	−41.4	−74	−41.4
40–49	454	0	0.1	−283	−38.4	−283	−38.4
50–64	3035	58	1.9	−832	−21.5	−774	−20.3
⩾65	4602	37	0.8	−479	−9.4	−441	−8.7
All ages	8195	95	1.2	−1667	−16.9	−1571	−16.1
Ovary							
<40	445	0	0.0	−94	−17.4	−94	−17.4
40–49	706	7	1.0	−172	−19.6	−165	−18.9
50–64	2004	28	1.4	−282	−12.3	−254	−11.2
⩾65	3665	13	0.4	−156	−4.1	−143	−3.8
All ages	6820	48	0.7	−703	−9.3	−655	−8.8

Abbreviations: HRT = hormone replacement therapy (postmenopausal hormones); PAF = population-attributable fraction.

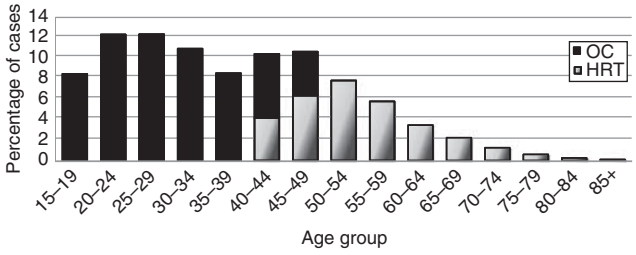

Figure 3 Fraction of breast cancer cases attributable to hormones, by age, UK 2010.

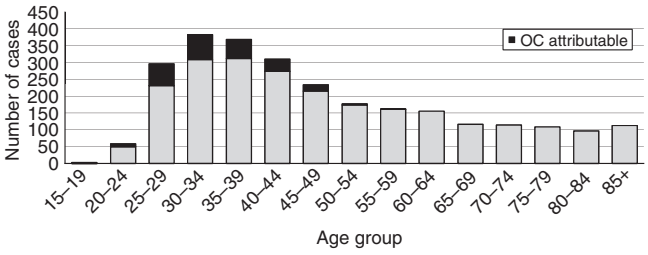

Figure 4 Cervix cancer: total number of cases and those attributable to OC use, UK, 2010.

hormone use is 1.2%, with the highest attributable fraction (2.5%) being in age group 55–59.

Figure 5 illustrates the net effects of OCs and post-menopausal hormones (HRT) by age group.

Ovarian cancer Although there is a small increase in risk of ovarian cancer in post-menopausal women using hormonal preparations (the PAF is 0.7%), this effect is overwhelmed by the longstanding protection provided by current and past use of OCs, which are estimated to be preventing 9.3% of the ovarian cancers that would otherwise have occurred (Table 6).

Figure 6 illustrates the net effects of OCs and post-menopausal hormones (HRT) by age group. Overall in 2010, there would be some 655 fewer cases of ovarian cancer than would have been the

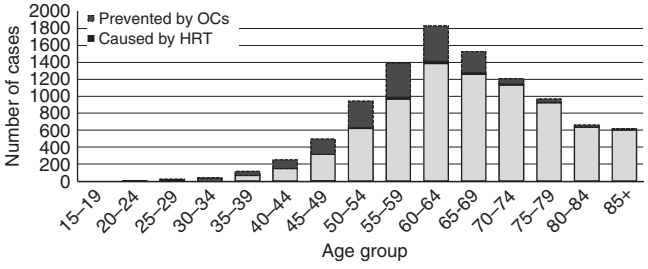

Figure 5 Endometrial cancer: observed cases, including number caused by HRT, and the number estimated to be prevented by current and past use of oral contraceptives (OCs), UK, 2010.

case if there had been no use of exogenous hormones (as OCs or as post-menopausal hormonal therapy).

Summary

Table 7 summarises the results. Overall, a net total of 1675 cancers occurring in 2010 in the UK can be attributed to current or past use of post-menopausal hormonal preparations by women, representing 1.1% of all cancers in women (0.5% for both sexes). However, the net effect of the use of OCs is *protective* – with almost 1600 fewer cancers than would have been the case if they had not been used.

The net effect of hormone use is therefore very tiny – just 102 cases attributable to their use.

DISCUSSION

In this paper, we used the RR of cancer in relation to use of post-menopausal hormones from the Million Women Study (Beral, 2003; Beral *et al*, 2005, Million Women Study Collaborators, 2007) to estimate the likely impact of hormone use on the number of cancer cases at ages >45 in the UK in 2010. This study recorded the use of HRT in women aged 50–64 at the time of enrolment, and followed them for an average of 2.6 years for breast cancer incidence, 3.4 years for incidence of endometrial cancers and 5.3 years for ovarian cancers. For breast cancer, the risk among women who were current users of HRT was 1.66, a result not very different from that observed in the Women's Health Initiative randomised trial for women aged 50–79, in whom the risk of breast cancer in women taking oestrogen plus progesterone was 1.49 after an average 5.6 years of follow-up; the excess relative to the placebo group emerged after 3 years, and continued to widen until the maximum follow-up period of 7 years (Chlebowski *et al*, 2003). The RRs in the EPIC study (Bakken *et al*, 2011) after a mean follow-up of 8.6 years were 1.42 for current users of oestrogen-only and 1.77 for current users of combined preparations. For ovarian cancer, the risks observed in the Million Women Study were very similar to those in the meta-analyses of Zhou *et al* (2008) and Pearce *et al* (2009). With respect to endometrial cancer, however, the EPIC study (Allen *et al*, 2010) found rather higher risks for current users of hormone therapy after 9 years of follow-up than the Million Women Study (2.52 for oestrogen-only HT, 2.96 for tibolone and 1.41 for combined oestrogen–progestogen (although risks differed according to regimen and type of progestogen constituent).

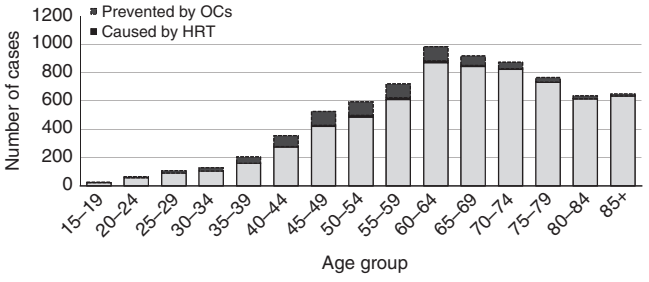

Figure 6 Ovarian cancer: observed cases, including the number caused by HRT and those estimated to be prevented by current and past use of oral contraceptives (OCs), UK, 2010.

As an increased risk of breast and endometrial cancer is observed in past users of at least some hormonal preparations by post-menopausal women, it is important to take this into account, especially as the prevalence of current use has been falling dramatically in the UK since around 2000–1 (Figure 2, Watson *et al*, 2007). In fact, we have no information on prevalence of ex-users in the population, and can only estimate it in terms of the difference in population prevalence from one year to the next, which is surely an underestimate. On the other hand, prevalence of use of hormonal preparations is calculated by dividing the number of women who receive prescriptions for hormonal preparations by the number at risk (in the General Practice Research Database), and this prevalence is assumed to apply to the UK population. In fact, it is possible that many women who receive hormonal preparations have had a hysterectomy, and so would not be at risk of endometrial cancer, so that the attributable fractions for this cancer are overestimated.

Current and recent use of OCs increase the risk of breast and cervical cancer, and decrease the risk of endometrial and ovarian cancer, the latter effects lasting 20 years or more. Although the data on current use of oral contraception should be accurate, information on past use is much less certain, and estimates were based on published data from recent UK studies. The protective effect of OCs is considerably greater with respect to endometrial cancer, as might be expected from the markedly reduced risks in current and past users (IARC, 2007). Pike's (1987) model of the effect of hormones on cancers of the female reproductive organs estimates that 5-year use of oral contraception delays the rise in age-specific incidence of endometrial cancer by 5 years, thus producing lower rates at older ages. On this basis, Key and Pike (1988) predicted that 5-year use of combined OCs beginning at age 28 would produce a 60% reduction in lifetime risk.

It seems that OCs are beneficial not only in preventing unwanted pregnancy but also, on balance, in reducing the numbers of cancers that would otherwise have occurred. For this reason, in the final summary section (Section 16) we include only post-menopausal hormone therapy as a risk factor contributing to cancers in the UK.

See acknowledgements on page Si.

Conflict of interest

The author declares no conflict of interest.

Table 7 Estimated cases of cancer occurring in women in 2010, and the fraction attributable to hormone exposures

	All cancer cases by type of hormone exposure[a]						
		HRT		Oral contraceptives		Both	
Age (years)	Observed cases	Excess attributable cases	PAF (%)	Excess attributable cases	PAF (%)	Excess attributable cases	PAF (%)
<40	8140	0	0.0	228	2.8	228	2.8
40–49	13 667	384	2.8	−58	−0.4	326	2.4
50–64	41 338	1006	2.4	−1109	−2.6	−103	−0.2
⩾65	92 439	285	0.3	−634	−0.7	−349	−0.4
All ages	155 584	1675	1.1	−1573	−1.0	102	0.1

Abbreviations: HRT = hormone replacement therapy (postmenopausal hormones); PAF = population-attributable fraction. [a]Excluding non-melanoma skin cancer.

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