Association of Combined Estrogen–Progestogen and Progestogen-Only Contraceptives with the Development of Cancer

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Abstract

Combined estrogen–progestogen contraceptives (oral contraceptives or OCs) and progestogen-only contraceptives (POCs) are synthetic steroids that bind to steroid hormone receptors, which are widespread throughout the body. They have a profound effect on cellular physiology. Combined OCs have been classified by the International Agency for Research on Cancer (IARC) as Group 1 carcinogens, but their findings have not been updated recently. In order to update the information and better understand the impact that OCs and POCs have on the risk of development of cancers, a comprehensive literature search was undertaken, focusing on more recently published papers. In agreement with the IARC, the recent literature confirms an increased risk of breast cancer and cervical cancer with the use of OCs. The recent literature also confirms the IARC conclusion that OCs decrease the risk of ovarian and endometrial cancers. However, there is little support from recent studies for the IARC conclusion that OCs decrease the risk of colorectal cancer or increase the risk of liver cancer. For liver cancer, this may be due to the recent studies having been performed in areas where hepatitis is endemic. In one large observational study, POCs also appear to increase the overall risk of developing cancer. OCs and POCs appear to increase the overall risk of cancer when carefully performed studies with the least intrinsic bias are considered.

Summary: OCs have been classified as cancer-causing agents, especially leading to increases in breast cancer and cervical cancer. A review of the recent scientific literature was performed to see whether this still appears to be the case. The recent literature supports the cancer-causing role of OCs especially for breast cancer and cervical cancer. Studies also indicate that progesterone-only contraceptives (such as implants and vaginal rings) also can cause cancer. This is especially true for breast cancer and cervical cancer.

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Combined estrogen–progestogen oral contraceptives (OCs) have been classified as Group 1 carcinogens by the World Health Organization (Cogliano et al. 2005). They are comprised of potent synthetic steroids that act on the estrogen or progesterone receptors. It is estimated that 15.9 percent of all women in the United States aged fifteen to forty-four, or ten million women, are currently using OCs, while another 2.6 percent are using progestogen-only contraceptives (POCs; Centers for Disease Control 2018). Of women aged fifteen to forty-four, 79.3 percent have at some point used OCs. These steroid agonists have numerous effects on the body as estrogen and progesterone receptors are widely expressed in the body, especially in reproductive tissues. However, they are also known to be expressed in immune cells and many other tissues (see Genecards ESR1; Genecards ESR2; Genecards PGR). As such, it can be expected that OCs and POCs can have direct or indirect effects on numerous cells and tissues. This can include both short-term effects (such as prevention of ovulation and thinning of the endometrium) and long-term effects (as a result of effects on cellular growth, metabolism, immunomodulation, etc.). Two long-term effects of the use of OCs and POCs are impacts on cell division and immune responses, both of which can increase or decrease the susceptibility to cancer. The IARC classification of OCs as Group 1 carcinogens was an upgrade from their previous classification. (IARC 2007). The data for this monograph were updated a few years later and include studies published up to May 2008. Their conclusion was:

There is *sufficient evidence* in humans for the carcinogenicity of combined estrogen–progestogen OCs. Combined estrogen–progestogen OCs cause cancer of the breast, in situ and invasive cancer of the uterine cervix, and cancer of the liver.

For cancer of the endometrium, ovary, and colorectum, there is *evidence suggesting lack of carcinogenicity*. An inverse relationship has been established between exposure to combined estrogen–progestogen OCs and cancer of the endometrium, ovary, and colorectum.

There is sufficient evidence in experimental animals for the carcinogenicity of several combinations of estrogen–progestogen used in OCs.

Combined estrogen–progestogen OCs are *carcinogenic to humans* (Group 1; IARC 2012).

In order to update the information and better understand the impact that OCs and POCs have on the risk of development of cancers, a comprehensive literature search was undertaken, focusing on papers published since 2005. As the chemical components of OCs have changed over the years, the decision was made to focus on the most recent literature as this was felt to be most relevant to the currently available agents. We also sought to compare our results with the most recently published IARC monograph and reevaluate their conclusions with the most recent data.

Materials and Methods

The objective of this literature survey was to determine whether OCs and POCs alter the susceptibility for cancers. The search was performed in the PUBMED database for the following terms:

Contraceptive OR contraceptives OR contraception OR levonorgestrel OR etonogestrel OR ethinyl estradiol OR estradiol valerate OR dienogest OR drospirenone OR norelgestromin
AND
Cancer

A search performed on May 3, 2017, returned 17,144 papers. The search was then limited as follows:

Title or abstract for: contraceptive OR contraceptives OR contraception OR levonorgestrel OR etonogestrel OR ethinyl estradiol OR estradiol valerate OR dienogest OR drospirenone OR norelgestromin

Title for: cancer

A total of 2,422 papers were returned. The search was further limited to humans, and 2,195 papers

were returned. Titles were reviewed back to the year 2000, and a total of 434 papers were selected for more in-depth review. The papers published since 2005 were the primary focus of this review.

Each paper was rated based on the parameters noted in the strengthening the reporting of observational studies in epidemiology (STROBE) statement (von Elm et al. 2007). This included the following:

- Background and rationale provided?
- Objectives stated?
- Key elements of study design presented?
- Setting, locations, and relevant dates described?
- Eligibility criteria and the sources and methods of selection of participants provided?¹
- Matching criteria and number of exposed/unexposed/controls provided?
- Diagnostic criteria, outcomes, exposures, predictors, potential confounders, and effect modifiers provided?
- Sources of data and details of methods of assessment provided?
- Any efforts to address potential sources of bias?
- Rationale for the study size provided?
- Information on how quantitative variables were handled in the analyses?
- Statistical methods described, including those that control for confounding?
- Methods used to examine subgroups and interactions described?
- Missing data addressed?¹
- How were lost to follow-up addressed (cohort studies)?¹
- How was matching of cases and controls addressed?
- Sensitivity analyses described?
- Numbers of individuals at each stage of the study provided and reasons for nonparticipation?¹
- Characteristics of study participants, information on exposures, and potential confounders provided?
- Number of participants with missing data for each variable of interest provided?¹
- Follow-up time provided (cohort studies)?¹
- Numbers of outcome events or summary measures over time reported (cohort studies)?¹
- Numbers in each exposure category or summary measures of exposure reported (case-control studies)?
- Unadjusted estimates and confounder-adjusted estimates provided with their precision?

- Other analyses reported (i.e., subgroups)?
- Limitations of the study discussed, including magnitude and direction of potential bias?
- Source of funding provided?

Each item was assigned a maximum score of 1, and the result converted into a percentage. Also noted for each study were the odds ratio (OR), relative risk (RR), or hazard ratio (HR), and the 95 percent confidence interval. Briefly, for RR, if the population under study is divided into those with and without exposure to a steroidal contraceptive and is further divided into those who subsequently develop the disease or do not develop the disease, the RR is the percentage of those in the exposed group with the disease divided by the percentage of those in the unexposed group who develop the disease. The OR is the proportion of those in the exposed group who did versus did not develop the disease divided by the proportion of those in the unexposed group who did versus did not develop the disease (Altman 1991; Deeks and Higgins 2010; Pagano and Gauvreau 2000; Parshall 2013). A HR is the ratio of the hazard rates corresponding to the conditions described by two levels of an explanatory variable (Spruance et al. 2004). For example, if the death rate in population A is twice that in population B, the HR for A versus B would be 2. For all studies, if both unadjusted and multivariable-adjusted ORs, RRs, or HRs were stated, the multivariable-adjusted ORs, RRs, or HRs were summarized here.

Results

Breast Cancer

Breast cancer is the most commonly diagnosed cancer (excluding nonmelanoma skin cancers) in women in developed nations, including the United States, with 1.7 million cases diagnosed worldwide annually. It accounts for 30 percent of all new cancer diagnoses in women (https://www.breastcancer.org/symptoms/understand_bc/statistics). According to the Surveillance, Epidemiology and End Results (SEER) statistics (<https://seer.cancer.gov/statfacts/html/breast.html>), it is estimated that there are about 3,418,000 women with invasive breast cancer in the United States. There will be about 266,000 new cases of breast cancer in 2018, accounting for 15.3 percent of all new cancer cases, with about 41,000 deaths, accounting for 6.7 percent of all cancer deaths. The five-year survival for breast cancer is 90 percent. Nulliparity or late childbearing and high body mass index are risk factors for breast cancer as

is exposure to OCs and hormone replacement therapy (HRT). Any risk factors that are controllable should be minimized. The data for breast cancer are shown in Table 1, split into cohort studies (Table 1), meta-analyses (Table 2), and case-control studies (Table 3). Women carrying the *BRCA1* and *BRCA2* genes comprise a high-risk group and account for 10–15 percent of all breast cancers. These women are often begun on OCs at an early age to reduce their risk of ovarian cancer. However, in a case-control study of 2,492 matched pairs of women with the *BRCA1* gene, OC use was associated with an increased risk of early onset breast cancer if begun under the age of twenty (OR = 1.45, 95 percent CI [1.20, 1.75]; Kotsopoulos et al. 2014) and the risk increased by 11 percent for each additional year of use.

The studies that looked at recent use (within one to five years) or current use of OCs in premenopausal women showed the most dramatic increased risk of breast cancer. In a case-control study, women aged twenty to forty-nine years with the use of OCs within a year had an increased risk of breast cancer (OR = 1.5; 95 percent CI [1.3, 1.9]; Beaber, Buist, et al. 2014). The same study showed an increase in risk depending on the formulation, with triphasic OCs carrying a markedly increased risk (OR = 3.1; 95 percent CI [1.4, 4.7]). In another large case-control study of women aged twenty to forty-five years, use of OCs for a year or more resulted in a 2.5-fold increased risk of triple negative breast cancer (95 percent CI [1.4, 4.3]) but not for the receptor positive breast cancers. In the same study, women aged forty years or younger with a year or more use of OCs had a higher RR of triple negative breast cancer (RR = 4.2; 95 percent CI [1.9, 9.3]; Dolle et al. 2009). A cohort study of over 35,000 postmenopausal women found a significantly increased risk of breast cancer in women on HRT if they had used OCs in the past (RR = 2.45; 95 percent CI [1.92, 3.12]) as compared with never users (RR = 1.67; 95 percent CI [1.32, 2.12]; Lund et al. 2007). There also appears to be an increased risk for African American women on OCs within the past five years for estrogen receptor (ER)+ cancers (OR = 1.46; 95 percent CI [1.18, 1.81]), for ER– cancers (OR = 1.57; 95 percent CI [1.22, 1.43]), and for triple negative cancers (OR = 1.78; 95 percent CI [1.25, 2.53]) with the risk of ER+ cancers continuing for fifteen to nineteen years after stopping the OCs (Betha et al. 2015).

In a French study (DeLort et al. 2007) of 934 women who developed breast cancer, the use of OCs increased the risk of early development of breast

cancer (OR = 1.84; 95 percent CI [1.38, 2.44]). However, initiating OCs after age twenty-three reduced the risk (OR = 0.52; 95 percent CI [0.34, 0.79]). Use of the levonorgestrel-releasing intrauterine device (IUD), commonly used to treat abnormal bleeding in the perimenopause, increased the risk of developing breast cancer in postmenopausal women (OR = 1.48; 95 percent CI [1.10, 1.99]; Heikkinen et al. 2016). The risk varies with the formulation, as the current use of a triphasic pill containing levonorgestrel carries an excess risk of causing breast cancer (RR = 3.05; 95 percent CI [2.00, 4.66]; Hunter et al. 2010). In a large prospective cohort study of 1.8 million Danish women aged fifteen to forty-nine, enrolled and followed from 1995 to 2012 through various national registries, the risk of breast cancer among current or recent users increased depending on length of use from an RR of 1.09 with less than one year of use (95 percent CI [0.96, 1.23]) to an RR of 1.38 (95 percent CI [1.26, 1.51]) for more than ten years of use (Mørch et al. 2017). They found the increased risk persisted after discontinuing use if OCs were used for five years or more. These investigators also found an increased risk in current or recent use of the progestogen-only intrauterine device (RR = 1.21; 95 percent CI [1.11, 1.33]).

There is very little literature on the risk of cancer with the POCs. Only 2 percent of women report the use or ever use of POCs. In a study of 4,816 women with breast cancer, 135 of whom had used POCs, there was a better long-term survival with POC use (Samson et al. 2017) as compared with combined oral contraceptive(s) (COC) use. However, the investigators acknowledged the small sample.

OCs were illegal until 1999 in Japan, and as of 2015, only 5 percent of women in that country use OCs. In a recent Japanese study of 155 cases of breast cancer, there was no increased risk of breast cancer with OC use (Ichida et al. 2015) as compared with controls (OR = 0.45; 95 percent CI [0.22, 0.90]). They acknowledged the need for further long-term prospective studies.

Cervical Cancer

According to the SEER statistics (<https://seer.cancer.gov/statfacts/html/cervix.html>), it is estimated that there are 257,524 women in the United States with cervical cancer. There will be about 13,000 new cases of cervical cancer in 2018, with about 4,000 deaths. The five-year survival for cervical cancer is 66 percent. The data for cervical cancer are shown in Table 4. All studies appear to be in agreement that

Table 1. Breast Cancer (Cohort Studies).

Study	Study Design	OR ^a		RR ^b		OR		RR		Cases	Controls	Quality Score (%)	
		Ever Use	Current Use	Ever Use	Current Use	Past Use	Current Use	Past Use	RR				
Mørch et al. (2017)	Cohort			1.2 ^c (1.14–1.26)						1,797,932	^d	100	
Heikkinen et al. (2016)	Cohort			1.37 (1.12–1.68)						7,000	20,000	100	
Lund et al. (2007)	Cohort			1.33 (1.11–1.59)						11,777	23,676	96	
Poosari et al. (2014)	Cohort			1.31 (0.65–2.65)						70	11,344	92	
Phipps et al. (2011)	^e			0.80 ^f (0.68–0.94)						5,194		92	
Brohet et al. (2007) ^g	Cohort			1.47 (1.16–1.87)						846	747	88	
Thorbjarnardottir et al. (2014)	Cohort			1.32 (1.02–1.70)						654	16,928	84	
Samson et al. (2017)	Cohort			1.80 ^h (1.29–2.55)						4816		83	
Rosenberg et al. (2010)	Cohort			1.65 (1.19–2.30)						789	53,848	83	
Silvera, Miller, and Rohan (2005)	Cohort			0.88 ^h (0.73–1.07)						1,707	25,611	78	
Hunter et al. (2010)	Cohort			1.12 (0.95–1.33)			1.33 (1.03–1.73)			1,344	115,264	73	
				1.42 ⁱ (1.05–1.94)									
				3.05 ^j (2.00–4.66)									
Trivers et al. (2007) ^k	Cohort				1.57 (0.95–2.61)					292 ^l	1,264 ^m	67	

^aOR = odds ratio (95 percent confidence interval).

^bRR = relative risk (95 percent confidence interval).

^cInitiation before age twenty, greater than ten years of use and evaluation within five years of stopping further increased the risk.

^dEntire population of Denmark was the cohort.

^eConcurrent randomized clinical trials and an observational study.

^fHazard ratio are shown. Note that women started oral contraceptives (OCs) after age twenty-five had been off OCs for many years.

^gEvaluation in patients carrying BRCA mutations. Hazard ratios are shown.

^hHazard ratios are shown.

ⁱEight or more years of use.

^jLevonorgestrel containing combined oral contraceptives.

^kLooked at mortality in patients with breast cancer over eight to ten years depending on whether they were on OCs at the time of diagnosis or within one year.

^lDeaths.

^mTotal cohort.

Table 2. Breast Cancer (Case-Control Studies).

Study	Study Design	OR ^a		RR ^b		OR		RR		Cases	Controls	Quality Score (%)
		Ever Use	Ever Use	Ever Use	Ever Use	Current Use	Past Use	Current Use	Past Use			
Dolle et al. (2009)	Case control	2.5 (0.9–5.24)				4.2 (1.9–9.3)				898	961	100
Lee et al. (2008)	Case case ^c	0.68 (0.33–1.38)								94	444	100
Sweeney et al. (2007)	Case control	1.27 (0.99–1.63)								2,318	2,515	100
Beaber, Malone, et al. (2014)	Case control	1.5 (1.1–2.2)								985	882	100
Li et al. (2012) ^d	Case control	2.2 (1.2–4.2)								1,028	919	96
Beaber, Buist, et al. (2014)	Case control					1.5 ^e (1.3–1.9)				1,102	21,952	96
Ichida et al. (2015)	Case control					0.45 (0.22–0.90)				155	12,333	96
Ma et al. (2010)	Case control	2.87 ^f (1.44–5.74)								1,197	2,015	95
Folger et al. (2007)	Case control	1.0 ^g (0.8–1.1)								4575	4,682	92
Jernström et al. (2005)	Case control						2.10 (1.32–3.33)			245	745	92
Kotsopoulos et al. (2014) ^h	Case control	1.45 ⁱ (1.20–1.75)								2,492	2,492	88
		1.19 (0.99–1.42)										
Figueiredo et al. (2010) ^k	Case control						2.38 (0.72–7.83)			705	1,398	86
Veneroso, Siegel, and Levine (2008)	Case case ^l	1.12 (1.03–1.23)								116	99	86
Ma et al. (2006)	Case control	1.27 ^m (0.75–2.14)					0.76 (0.49–1.18)			1,366	440	84
		0.76 ⁿ (0.49–1.18)										
Rosenberg et al. (2008)	Case control	1.5 ^o (1.2–1.8)								907	1,711	83
Haile et al. (2006)	Case control	0.77 ^p (0.53–1.12)								195	497	83
		1.62 ^q (0.90–2.92)								128	307	
Milne et al. (2005)	Case control	1.52 (1.22–1.91)								1,156	815	83
Amadou et al. (2013)	Case control	1.68 (0.67–4.21)								1,000	1,074	75
Ozmen et al. (2009)	Case control	0.60 (0.48–0.74)								1,492	2,167	74
Delort et al. (2007)	Population based ^r	1.84 ^s (1.38–2.44)								934		71
Beji and Reis (2007)	Case control	1.98 (1.38–2.85)								405	1,050	63

(continued)

Table 2. (continued)

Study	Study Design	OR ^a		RR ^b		OR		RR		Quality Score (%)
		Ever Use		Ever Use		Current Use	Past Use	Current Use	Past Use	
Veisy et al. (2015)	Case control	2.11 (1.44–3.08)							235	63
Tehrani et al. (2010)	Case control	2.83 (1.87–4.24)							321	58
Lumachi et al. (2010)	Retrospective review	2.06 (1.14–3.70)							404	33

Note: DMPA, depo-medroxyprogesterone acetate; PR, progesterone receptor.

^aOR = odds ratio (95 percent confidence interval).

^bRR = relative risk (95 percent confidence interval).

^cBRCA1 and BRCA2 carriers with breast cancer.

^dPopulation-based case control of women twenty to forty-four years with recent DMPA use for at least twelve months.

^eUse within the past year of oral contraceptives (OCs) increases the risk of breast cancer.

^fTriple negative breast cancer if less than eighteen years on OCs.

^gEvaluated short-term use only.

^hStudy of BRCA + patients.

ⁱLess than twenty years old.

^jTwenty to twenty-five years old.

^kEvaluation of BRCA1 and BRCA2 carriers; controls with unilateral breast cancer compared with contralateral cases.

^lComparison of more aggressive with less aggressive cases.

^mER –/PR –.

ⁿER +/PR +.

^oOR for five plus years of use.

^pBRCA1 + patients.

^qBRCA2 + patients.

^rPopulation-based study of early onset breast cancer.

^sOR for developing breast cancer two years earlier than nonusers.

Table 3. Breast Cancer (Meta-analyses).

Study	Study Design	OR ^a		RR ^b		OR		RR		Cases	Controls	Quality Score (%)
		Ever Use		Ever Use		Current Use		Current Use				
Bethea et al. (2015)	Meta-analysis	1.46 ^c	(1.18–1.81)							1,848	10,044	85
		1.57 ^d	(1.22–1.43)							1,043	10,044	
		1.78 ^e	(1.25–2.53)							494	10,044	
Zhu et al. (2012)	Meta-analysis	1.08 ^f	(0.99–1.17)									54
		1.36 ^h	(0.99–1.88)									
		1.51 ⁱ	(1.10–2.08)									
Moorman et al. (2013)	Meta-analysis	1.21 ^j	(0.93–1.58)									27

^aOR = odds ratio (95 percent confidence interval).

^bRR = relative risk (95 percent confidence interval).

^cER +.

^dER –.

^eTriple negative.

^fFor each five years on oral contraceptives the risk increased by 7 percent, but statistical significance not achieved.

^gStudy limited to BRCA1 and BRCA2 mutation carriers.

^hOne to three years of use.

ⁱ>Three years of use.

^jEight studies on BRCA1+ or BRCA2+ patients and breast cancer risk with COC use.

Table 4. Cervical Cancer.

Study	Study Design	OR ^a		RR ^b		OR		RR		Cases	Controls	Quality Score (%)
		Ever Use		Ever Use		Current Use	Past Use	Current Use	Past Use			
Roura et al. (2016)	Cohort study			1.1 ^c (0.9–1.3)		1.8 ^c (1.4–2.4)	1 ^c (0.9–1.3)			1,065	306,971	94
Leslie et al. (2014)	Case-control study	1.35 ^e (0.99–1.85)		1.6 ^d (1.1–2.3)		2.2 ^d (1.3–4.0)	1.6 ^d (1.1–2.2)			261	306,971	
McFarlane-Anderson et al. (2008)	Case-control study	1.59 ^f (0.87–2.82)								219	2,300	87
										240	102	83
Vanakankovit and Taneeapanichskul (2008)	Case-control study	2.48 ^g (1.30–4.74)								60	180	76
Wilson et al. (2013)	Case-control study	1.49 (0.79–2.64)										
Matos et al. (2005)	Case-control study	1.22 (0.96–1.56)								724	3,479	76
International Collaboration (2007) ^h	Case-control study	1.3 (0.8–3.1)								140	157	47
	Meta-analysis	1.05 ⁱ (1.04–1.07)								16,573	35,509	97
	<5 Years of use	0.96 (0.04) ^j										
	5–9 Years of use	1.2 (0.05) ^j										
	10+ Years of use	1.56 (0.08) ^j										
	<5 Years of use	1.07 (0.08) ^k										
	5+ Years of use	1.22 (0.11) ^k								7,227	19,335	

^aOR = odds ratio (95 percent confidence interval).
^bRR = relative risk (95 percent confidence interval).
^cIncludes cervical intraepithelial neoplasia grade 3, carcinoma in situ and invasive cervical cancer.
^dAnalysis limited to invasive cervical cancer.
^eStudy limited to HIV+ women.
^fCombined hormonal contraceptives.
^gProgestin-only contraceptives.
^hMeta-analysis of twenty-four studies (fifteen cohort and nine case-control studies).
ⁱRelative risk per year of use for current users of combined hormonal contraceptives.
^jFloating standard error shown for users of combined hormonal contraceptives.
^kProgestin-only contraceptives. Floating standard error are shown. The 95 percent confidence interval for five plus years of use is 1.01–1.46.

there is an increased risk of cervical cancer in users of OCs (OR apparently about 1.05 *per year of use*), and this risk increases with duration of use. Current use appears to confer a higher risk than past use, and the risk for invasive cancer shows the highest increase in risk (Roura et al. 2016). One case-control study (McFarlane-Anderson et al. 2008) and one meta-analysis (International Collaboration 2007) also showed an increased risk with POCs. Thus, there does appear to be an increased risk of cervical cancer in users of OCs or POCs, and the risk appears to increase with the duration of use.

Liver Cancer

According to the SEER statistics (<https://seer.cancer.gov/statfacts/html/livibd.html>), it is estimated that there are about 72,000 people with liver cancer in the United States including about 18,000 women. There will be about 42,000 new cases of liver cancer in 2018 (about 11,000 women), with about 30,000 deaths (about 7,800 women). The five-year survival for liver cancer is 18 percent. The data for liver cancer are shown in Table 5 One meta-analysis of fourteen case-control studies and three cohort studies failed to show a significant difference, although separate analysis of the case-control studies did show a significantly increased OR (1.55) (An 2015). Meta-analysis of the three cohort studies did not show an increased risk. One more recent cohort study did not show a significantly increased risk, while an older case-control study also did not. Thus, the recent studies reviewed do not confirm the earlier studies noted by IARC which concluded that OCs increase the risk of liver cancer. However, this difference may be attributed to the specific nature of the IARC findings. They noted that the risk of liver cancer was increased only in populations that had a low incidence of hepatitis B infection and chronic liver disease. The meta-analysis by An (2015) noted, “Chronic infections with hepatitis B or C virus and alcohol consumption are established risk factors for liver cancer. Few studies in original data clarified its effect. Thus, inadequate control of the confounders might mask the true risk” (p. 6). In the cohort study (McGlynn et al. 2015), they noted that of eighty-eight hepatocellular carcinoma cases evaluated, 31.7 percent were positive for anti-hepatitis C virus while another 2.3 percent were positive for hepatitis B surface antigen. Thus, these more recent studies appear to have been in populations where hepatitis virus infection was prevalent. Therefore, they do not adequately evaluate populations with a low incidence of hepatitis virus infection and chronic liver

Table 5. Liver Cancer.

Study	Study Design	OR ^a		RR ^b		OR		RR		Cases	Controls	Quality Score (%)
		Ever Use		Ever Use		Current Use	Past Use	Current Use	Past Use			
McGlynn et al. (2015)	Cohort study ^c			1.12 (0.82–1.55)						248	799,252	90
Chang et al. (2006)	Case-control study	0.95 (0.66–1.37)								360	3,186	83
An (2015) ^d	Meta-analysis study	1.2 ^d (0.93–1.63)								1,798	1,118,599	92
		1.55 ^e (1.04–2.31)		0.88 ^f (0.64–1.22)						1,055	6,149	
										743	1,111,707	

^aOR = odds ratio (95 percent confidence interval).
^bRR = relative risk (95 percent confidence interval).
^cConsortium of eleven cohort studies.
^dMeta-analysis of fourteen case-control and three cohort studies.
^eCase-control studies.
^fCohort studies.

disease. Thus, these data do not seem sufficient to contravene the IARC conclusion that OCs may cause liver cancer.

Endometrial Cancer

According to the SEER statistics (<https://seer.cancer.gov/statfacts/html/corp.html>), it is estimated that there are about 727,000 women with uterine cancer in the United States. There will be about 63,000 new cases of uterine cancer (almost all endometrial) in 2018, with about 11,000 deaths. The five-year survival for uterine cancer is 81 percent. The data for endometrial cancer are shown in Tables 6, 7 and 8. Numerous studies show a decreased incidence of endometrial cancer with the use of hormonal contraceptives with almost all studies focusing on combined estrogen and progestogen preparations. There is a clear trend with longer use being associated with lower incidence. The incidence on an annualized basis is 0.95 for use of combined agents (Hüsing et al. 2016; Cook et al. 2014). Beginning OCs prior to or after the first pregnancy does not seem to have an effect (Schonfeld et al. 2013). The meta-analyses and best cohort studies seem to indicate an overall OR of about 0.75.

Ovarian Cancer

According to the SEER statistics (<https://seer.cancer.gov/statfacts/html/ovary.html>), it is estimated that there are about 225,000 women with ovarian cancer in the United States. There will be about 22,000 new cases of ovarian cancer in 2018, accounting for 1.3 percent of all new cancer cases, with about 14,000 deaths, accounting for 2.3 percent of all cancer deaths. The five-year survival for ovarian cancer is 47 percent. The data for ovarian cancer are shown in Tables 9, 10 and 11. Most of the studies showed a significant decrease in risk with the ever use of OCs. Thus, there does appear to be a protective effect of OCs on the risk of ovarian cancer. Based on the most reliable studies, the RR for ever use of OCs for ovarian cancer is 0.84–0.86 (Tsilidis et al. 2011; Fortner et al. 2015). The RR per five years of use is 0.87 (0.82–0.93). For those with BRCA1 or BRCA2 mutations, the risk reduction is even greater: 0.21–0.63 (Kotsopoulos et al. 2015; McLaughlin et al. 2007; Perri et al. 2015). A couple of studies (Kurta et al. 2012; Greer et al. 2005) found that even six months or less of OC use decreased risk (OR = 0.88 and 0.73, respectively). And while Wilailak et al. (2012) found a decreased risk in Thailand with less than one year of use (OR = 0.86), Gay

et al. (2015) found an increased risk in Singapore (HR = 1.16), as did Moorman et al. (2009) in both whites and African Americans in North Carolina (OR = 1.18 and 1.89, respectively). Interestingly, Moorman et al. (2009) showed that the risk reduction is greater for African American women than for white women (0.52 vs. 0.73 with five plus years of use, respectively). Yang et al. (2012) found a decreased risk of serous (RR = 0.69), endometrioid (RR = 0.69), and other (RR = 0.70) ovarian cancers but an increased risk of mucinous (RR = 1.72) and clear cell (RR = 1.47) ovarian cancers. However, Pearce et al. (2013), while finding a similar decreased risk in serous and endometrioid ovarian cancers, also found a decreased risk in mucinous (OR = 0.68) and clear cell (OR = 0.4) ovarian cancers. Another study (Arab et al. 2010) noted that the ovarian cancer rate in Iran is 76 percent lower than in developed countries. Arab et al. noted that OCs lower ovarian cancer risk and concluded that OC use should be encouraged in order to keep the rate of ovarian cancer constant or decreasing. However, if one looks at the rate of contraceptive use in Iran compared to North America, the rates are similar (Iran 15.6 percent of married/in union women; North America 16.5 percent; Europe 21.9 percent; United Nations, Department of Economic and Social Affairs, Population Division 2015). This seems to indicate that there is something other than OCs keeping the ovarian cancer rate low (perhaps parity, which is known to decrease ovarian cancer risk). Also the increased risk of the more prevalent breast cancer would not support the encouragement of OC use, and so the authors' conclusion does not follow. This study could not be included in this review as it lacked ORs.

Colorectal Cancer

According to the SEER statistics (<https://seer.cancer.gov/statfacts/html/colorect.html>), it is estimated that there are about 1,332,000 people with colorectal cancer in the United States including about 577,000 women. There will be about 140,000 new cases of colorectal cancer in 2018 (about 61,000 in women), with about 51,000 deaths (about 22,000 women). The five-year survival for colorectal cancer is 65 percent. The data for colorectal cancer are shown in Tables 12, 13 and 14. The data are arranged by type of study, with cohort studies shown first, then case-control studies, and finally meta-analyses. Although two meta-analyses showed a significant decreased risk with ever use of OCs (Luan et al. 2015; Bosetti et al. 2009), five of the seven recent

Table 6. Endometrial Cancer (Cohort Studies).

Study	Study Design	OR ^a		RR ^b		OR		RR		Cases	Controls	Quality Score (%)
		Ever Use		Ever Use		Current Use		Current Use				
Pfeiffer et al. (2013)	Cohort studies			1.44 ^c (1.29–1.62)						1,155	599	93
Hüsing et al. (2016)	Cohort study			0.95 ^d (0.93–0.96)						855	184,430	88
Dossus et al. (2010)	Cohort study			0.65 ^e (0.56–0.75)						1,017	301,601	83
Wernli et al. (2009)	Cohort study			0.7 (0.43–1.14)						206	259,434	67
Setiawan et al. (2007)	Cohort study			0.96 ^f (0.71–1.30)						321	46,612	73
				0.6 ^g (0.39–0.91)								
Vessey and Painter (2006)	Cohort study			0.1 (0.0–0.4)						77	14,828	57
Vessey and Yeates (2013) ^h	Cohort study			0.5 (0.3–0.7)								57

Note: COC, combined oral contraceptive.

^aOR = odds ratio (95 percent confidence interval).

^bRR = relative risk (95 percent confidence interval).

^cStudy limited to women aged fifty years or older. RR is shown for the risk of *not* using COCs for at least one year.

^dAnnualized relative risk.

^eHazard are ratios shown.

^fLess than five years of use.

^gFive plus years of use.

^hAdditional follow-up on the Vessey and Painter (2006) paper.

Table 7. Endometrial Cancer (Case-Control Studies).

Study	Study Design	OR ^a		RR ^b		OR		RR		Cases	Controls	Quality Score (%)
		Ever Use	Ever Use	Ever Use	Ever Use	Current Use	Past Use	Current Use	Past Use			
Cook et al. (2014)	Case-control study	0.95 ^c	(0.92–0.98)							524	1,032	94
Tao et al. (2006)	Case-control study	0.75	(0.60–0.93)							1,204	1,212	92
Segev et al. (2015)	Case-control study	1.49	(0.74–2.99)							83	1,027	86
Maxwell et al. (2006)	Case-control study	0.21 ^d	(0.10–0.43)							434	2,557	83
Maxwell et al. (2006)	Case-control study	0.39 ^e	(0.25–0.60)							434	2,557	83%
Zucchetto et al. (2009)	Case-control study	0.64	(0.43–0.96)							454	908	82
Rota et al. (2016)	Case-control study	0.65	(0.52–0.81)							1,449	3,811	77
Weiss et al. (2006)	Case-control study									1,304	1,779	68
		1.2 ^f	(0.9–1.5)							500	1,779	
		0.7 ^g	(0.6–0.9)							650	1,779	
		0.6 ^h	(0.4–0.9)							131	1,779	
Polesel et al. (2009)	Case-control studies (pooled)					0.56	(0.45–0.71)			1,446	4,076	66
Torres et al. (2012)	Case-control study	0.18	(0.08–0.45)							90	172	62
Okamura et al. (2006)	Case-control study	0.16	(0.04–0.66)							155	87	58

^aOR = odds ratio (95 percent confidence interval).

^bRR = relative risk (95 percent confidence interval).

^cAnnualized relative risk.

^dHigh potency progestin.

^eLow potency progestin.

^fLow tumor aggressiveness.

^gModerate tumor aggressiveness.

^hHigh tumor aggressiveness.

Table 8. Endometrial Cancer (Meta-analyses).

Study	Study Design	OR ^a		RR ^b		OR		RR		Cases	Controls	Quality Score (%)
		Ever Use	Ever Use	Ever Use	Ever Use	Current Use	Past Use	Current Use	Past Use			
Collaborative Group on Epidemiological Studies on Endometrial Cancer (2015) Cote et al. (2015)	Meta-analysis			0.76 ^c	(0.73–0.78)					27,276	115,743	95
	Meta-analysis			1.09 ^d	(0.85–1.40)					516	1,495	87
Schonfeld et al. (2013)	Meta-analysis	0.76 ^f	(0.58–1.00)	1.02 ^e	(0.95–1.10)					5,693	19,297	
	Meta-analysis	0.75 ^g	(0.67–0.85)							360	26,576	86
										1,378	145,205	

^aOR = odds ratio (95 percent confidence interval).

^bRR = relative risk (95 percent confidence interval).

^cRelative risk per five years of use.

^dAnalysis of black women.

^eAnalysis of white women.

^fNulliparous women.

^gParous women.

Table 9. Ovarian Cancer (Cohort Studies).

Study	Study Design	OR ^a		RR ^b		OR		RR		Cases	Controls	Quality Score (%)
		Ever Use		Ever Use		Current Use	Past Use	Current Use	Past Use			
Tsilidis et al. (2011)	Cohort			0.86 ^c (0.73–1.00) 0.87 ^d (0.82–0.93)						878	326,518	93
Fortner et al. (2015)	Cohort			0.84 ^e (0.73–0.96)						1,104	333,022	92
Huang et al. (2015)	Cohort			1.02 ^c (0.69–1.51)						174	70,085	92
Soini et al. (2014)	Registry	0.6 ^f (0.45–0.76)								59	104,842	88
Gay et al. (2015)	Cohort			0.85 ^c (0.57–1.27) 0.94 ^g (0.85–1.02)						107	28,094	85
Yang et al. (2012)	Cohort			0.74 (0.63–0.87)						849	168,542	85
Braem et al. (2010) ^h	Cohort			0.71 ^c (0.52–0.97)						375	2,331	84
Tworoger et al. (2007)	Cohort			1.12 ⁱ (0.90–1.38) 0.97 ^j (0.66–1.41)						612	107,900	84
Antoniou et al. (2009) ^m	Cohort			0.75 ^k (0.54–1.05) 0.62 ^l (0.37–1.04)						253	3,066	81
Dorjgochoo et al. (2009)	Cohort			0.55 ^c (0.40–0.76)						94	64,411	75
Vessey and Painter (2006)	Cohort			1.1 (0.66–1.84)						106	16,926	57
Vessey and Yeates (2013) ⁿ	Cohort			0.3 (0.1–0.5) 0.5 (0.4–0.7)						143	16,889	57

^aOR = odds ratio (95 percent confidence interval).^bRR = relative risk (95 percent confidence interval).^cHazard ratios are shown.^dTrend per five years of use.^eLimited to invasive epithelial ovarian cancer. Hazard ratios are shown.^fWomen using the levonorgestrel intrauterine-releasing system for heavy menstrual bleeding, one or more purchase.^gAnnualized rate is shown.^hStudy of postmenopausal women.ⁱThree or fewer years of use.^jLess than three to five years of use.^kGreater than five to ten years of use.^lOver ten years of use.^mStudy of BRCA1 and BRCA2 carriers.ⁿAdditional follow-up to the Vessey and Painter (2006) paper.

Table 10. Ovarian Cancer (Case-Control Studies).

Study	Study Design	OR ^a		RR ^b		OR		RR		Cases	Controls	Quality Score (%)
		Ever Use	OR ^a	Ever Use	RR ^b	Current Use	Past Use	Current Use	Past Use			
Kotsopoulos et al. (2015) ^c	Case control	0.94 ^d (0.92–0.96)								1,329	5,267	94
Le et al. (2014)	Case control	0.95 ^e (0.92–0.97)										
		0.93 ^f (0.90–0.97)										
		0.94 ^g (0.55–1.63)								608	335	93
		0.56 ^h (0.37–0.84)										
		0.66 ⁱ (0.46–0.95)										
McLaughlin et al. (2007)	Case control	0.53 ^j (0.43–0.66)								799	2,424	93
Perri et al. (2015)	Case control	0.95 ^k (0.92–0.97)										
Bodmer et al. (2011)	Case control	0.21 ^l (0.14–0.31)								648	416	91
		0.94 ^m (0.78–1.14)								1,611	9,170	89
Lurie et al. (2008)	Case control	0.84 ⁿ (0.56–1.27)										
		0.59 (0.42–0.84)								813	992	89
Faber et al. (2013)	Case control	0.95 ^d (0.92–0.98)										
		0.68 ⁿ (0.53–0.88)								554	1,564	88
Kurta et al. (2012) ^p	Case control	0.97 ^o (0.45–2.14)										
		0.88 ^q (0.65–1.18)								902	1,802	88
Greer et al. (2005) ^y	Case control	0.69 ^r (0.53–0.89)										
		0.61 ^s (0.47–0.79)										
		0.63 ^t (0.48–0.82)										
		0.37 ^u (0.27–0.52)										
		0.73 ^w (0.54–0.99)										
		1.00 ^x (0.67–1.50)								608	926	86
		0.63 ^y (0.48–0.82)										
Wilailak et al. (2012)	Case control	0.66 (0.51–0.86)								330	982	86
Ferris et al. (2014)	Case control	0.35 (0.27–0.45)								389	5,643	85
Moorman et al. (2009)	Case control	OR for Whites								1,114	1,086	85
		OR for African Americans										
<1 Year of use		1.18 (0.82–1.69)										

(continued)

Table 10. (continued)

Study	Study Design	OR ^a		RR ^b		OR		RR		Cases	Controls	Quality Score (%)
		Ever Use		Ever Use		Current Use	Past Use	Current Use	Past Use			
	1–4 Years of use	0.78 (0.58–1.05)		0.72 (0.34–1.53)								
	5+ Years of use	0.73 (0.54–0.97)		0.52 (0.24–1.15)								
Ness et al. (2011)	Case control	0.67 (0.55–0.81)								902	1,800	85
Moorman et al. (2008)	Case control	0.5 ^z (0.3–0.8)								896	967	83
		0.8 ^{al} (0.6–1.1)										
Soegaard et al. (2007)	Case control	0.67 (0.53–0.85)								554	1,564	82
Pearce et al. (2013)	Case control	OR for invasive		OR for serous		OR for mucinous	OR for clear cell	OR for endometroid		5,566	7,374	78
	1 to <2 years of use	0.7 (0.59–0.83)		0.8 (0.65–0.98)		0.75 (0.36–1.57)	0.76 (0.46–1.24)	0.64 (0.45–0.92)				
	2 to <5 years of use	0.57 (0.50–0.65)		0.65 (0.56–0.77)		0.56 (0.35–0.90)	0.45 (0.34–0.60)	0.45 (0.34–0.60)				
	5 to <10 years of use	0.48 (0.42–0.55)		0.53 (0.45–0.62)		0.68 (0.46–1.01)	0.4 (0.27–0.58)	0.41 (0.31–0.54)				
	10+ years of use	0.34 (0.30–0.39)		0.39 (0.33–0.46)		0.48 (0.32–0.72)	0.28 (0.18–0.44)	0.28 (0.21–0.38)				
Pelucchi et al. (2007)	Case control	0.91 ^g (0.68–1.21)								1,822	4,631	78
		0.75 ^{all} (0.57–0.98)										
Chen et al. (2016) ^{all}	Case control	1.02 (0.45–2.29)								549	571	75
		0.46 (0.11–1.95)										
Collaborative Group on Epidemiological Studies of Ovarian Cancer (2008)	Case control	0.73 (0.70–0.76)								23,257	87,303	74

(continued)

Table 10. (continued)

Study	Study Design	OR ^a		RR ^b		OR		RR		Quality Score (%)
		Ever Use	0.80 (0.40–1.6)	Ever Use	0.74 (0.62–0.89)	Current Use	Past Use	Current Use	Past Use	
Le et al. 2012	Case control									72
Terada, Ahn, and Kessel (2016)	Case control							262	755	70
								486	77,730	

Note: CNV, copy number variation.

^aOR = odds ratio (95 percent confidence interval).

^bRR = relative risk (95 percent confidence interval).

^cStudy of "relationship between the cumulative number of ovulatory cycles (and contributing components) and the risk of developing ovarian cancer in BRCA mutation carriers."

^dAnnualized odds ratio.

^eAnnualized odds ratio for BRCA1 + patients.

^fAnnualized odds ratio for BRCA2 + patients.

^gLess than two years of use.

^hTwo to five years of use.

ⁱGreater than five years of use.

^jLimited to BRCA1 + and BRCA2 + patients.

^kAnnualized OR for BRCA1 + and BRCA2 + patients.

^lOne to fourteen prescriptions. Unadjusted ORs.

^mFifteen plus prescriptions. Unadjusted ORs.

ⁿCOCs.

^oProgestogen-only contraceptives.

^pStudy of women using fertility drugs.

^qGreater than six months of use.

^rSix to twenty-three months of use.

^sTwenty-four and fifty-nine months of use.

^tSixty to hundred and nineteen months of use.

^u120 + months of use.

^vResults were similar between a single use of oral contraceptive (OC) and multiple uses over each time period. This study also looked at reasons for stopping OC use and found that short-term use was protective only for women who stopped use because of side effects.

^wUp to six months of use.

^xSeven to twelve months of use.

^yThirteen plus months of use.

^zPremenopausal women at the time of diagnosis/interview.

^{aa}Postmenopausal women at the time of diagnosis/interview.

^{ab}Two plus years of use.

^{ac}Study of women with zero or one copy of CNV-67048 versus two copies.

Table 11. Ovarian Cancer (Meta-analyses).

Study	Study Design	OR ^a		RR ^b	OR		RR		Cases	Controls	Quality Score (%)
		Ever Use	Ever Use		Current Use	Past Use	Current Use	Past Use			
Poole et al. (2013)	Meta-analysis			0.69 ^c (0.55–0.88) 0.86 ^d (0.68–1.09)					4,342	267,282	86
Friebel et al. (2014, June)	Meta-analysis	0.40, 0.48, 0.56, 0.84 ^e		0.52143 ^f							85
	Meta-analysis	0.35, 0.39 ^g		1.04 ^h							85
Moorman et al. (2013)	Meta-analysis	0.58 (0.46–0.73)									84
Iodice et al. (2010)	Meta-analysis			0.5 ⁱ (0.33–0.75)					1,503	6,315	77

^aOR = odds ratio (95 percent confidence interval).

^bRR = relative risk (95 percent confidence interval).

^cRapidly fatal cancer.

^dLess aggressive cancer.

^eBRCA1 carriers, individual case-control studies, no meta-analysis performed.

^fBRCA1 carriers, single case-control study, no meta-analysis performed, hazard ratio are shown.

^gBRCA2 carriers, no meta-analysis performed.

^hBRCA2 carriers, single case-control study, no meta-analysis performed, hazard ratio are shown.

ⁱMeta-analysis of eighteen studies, limited to BRCA1+ or BRCA2+ patients.

high-quality cohort studies (counting the nurses health study I (NHSI) and nurses health study II (NHSII) study analyses as separate studies) failed to show any relationship between OC use and colorectal cancer. Two of the three case-control studies also failed to show an effect. Thus, these recent data do not appear to confirm prior studies, noted by IARC, that the use of OCs may reduce the risk of colorectal cancer. Interestingly, one study of anal cancer appeared to show an increased risk (Coffey et al. 2015).

Skin Cancer

According to the SEER statistics (<https://seer.cancer.gov/statfacts/html/melan.html>), it is estimated that there are about 1,222,000 people in the United States with melanoma of which about 455,000 are women. There will be about 91,000 new cases of melanoma in 2018 (about 34,000 new cases in women), with about 9,000 deaths (about 3,500 in women). The five-year survival for melanoma is 92 percent. The data for melanoma are shown in Table 15. Since 2005, only one review paper was identified which summarized the data from prior meta-analyses which did not show an increase or decrease in the risk of melanoma from the use of OCs. Thus, there does not appear to be convincing evidence of a decreased or increased risk of melanoma in users of OCs. Incidentally, one cohort study was evaluated which looked at the effect of OCs on nonmelanoma skin cancer (basal cell and squamous cell cancer). No effect of OCs was noted.

Thyroid Cancer

According to the SEER statistics (<https://seer.cancer.gov/statfacts/html/thyro.html>), it is estimated there are about 766,000 people in the United States with thyroid cancer of which approximately 571,000 are women. There will be about 54,000 new cases of thyroid cancer in 2018 (about 40,000 new cases in women), with about 2,000 deaths (about 1,500 in women). The five-year survival for thyroid cancer is 98 percent. The data for thyroid cancer are shown in Table 16. Most of the studies showed a lack of effect of OC use on the incidence of thyroid cancer, with the exception of the Schonfeld study (Schonfeld et al. 2011) that showed a significantly decrease RR for individuals using OCs for ten plus years and a meta-analysis (Wu and Zhu 2015), which included the Schonfeld study. However, two other meta-analyses showed no effect, and in the group that did show a significant effect in the Schonfeld study, only

fourteen cases of thyroid cancer were seen. In addition, in the Wu meta-analysis, they claimed to include 1,906 cases and about 1.3 million controls. Their analysis was clouded by the fact that they compared primarily longest duration of OC use versus shortest duration of use. This analysis appears to have excluded most cases they claimed to have analyzed. For example, in their inclusion of the Schonfeld study, they claimed 312 cases in 187,865 subjects, but only used the RR for those with ten plus years of use (fourteen cases and 17,269 subjects in total). They also weighted the studies, but it is unclear how they were weighted. Overall, there is no clear effect of OC use on the incidence of thyroid cancer.

Lung Cancer

According to the SEER statistics (<https://seer.cancer.gov/statfacts/html/lungb.html>), it is estimated that there are about 541,000 people with lung cancer in the United States, including about 232,000 women. There will be about 234,000 new cases of lung cancer in 2018 (about 100,000 women), with about 154,000 deaths (about 66,000 women). The five-year survival for lung cancer is 19 percent. The data for lung cancer are shown in Table 17. Most of the studies did not show a significant increase or decrease in risk with the ever use of OCs, although one study showed a decreased risk with ever use (Pesatori, Carugno, Consonni, Caporaso, et al. 2013). Thus, there does not appear to be an effect of OCs on the risk of lung cancer.

Kidney Cancer

According to the SEER statistics (<https://seer.cancer.gov/statfacts/html/kidrp.html>), it is estimated that there are about 505,000 people in the United States with kidney cancer including about 169,000 women. There will be about 65,000 new cases of kidney cancer in 2018 (about 22,000 women), with about 15,000 deaths (about 5,000 women). The five-year survival for kidney cancer is 75 percent. The data for kidney cancer are shown in Table 18. None of the studies show a significant increased risk with the ever use of OCs, and although one study showed a decreased risk with over ten years of use (Karami et al. 2013), others did not (Kabat et al. 2007). Thus, there does not appear to be an effect of OCs on the risk of kidney cancer.

Table 12. Colorectal Cancer (Cohort Studies).

Study	Study Design	OR ^a		RR ^b		OR		RR		OR		RR		Quality Score (%)
		Ever Use	OR ^a	Ever Use	RR ^b	Current Use	OR	Current Use	RR	Past Use	OR	Past Use	RR	
Tsilidis et al. (2010)	Cohort study				0.92 (0.83–1.02)									93
Zervoudakis et al. (2011)	Cohort study				1.04 (0.93–1.16)									92
Charlton et al. (2015)	Cohort study				1.01 ^c (0.91–1.12)									91
					1.03 ^d (0.69–1.53)									
Kabat, Miller, and Rohan (2008)	Cohort study				0.83 (0.73–0.94)									88
Coffey et al. (2015)	Cohort study	1.51 ^e (1.24–1.83)												87
Brändstedt et al. (2014)	Cohort study				1.05 (0.80–1.37)									83
Lin et al. (2007)	Cohort study				0.67 (0.50–0.89)									83

^aOR = odds ratio (95 percent confidence interval).

^bRR = relative risk (95 percent confidence interval).

^cNurses Health Study (NHS) I.

^dNHS II Study.

^eLimited to anal cancer.

Table 13. Colorectal Cancer (Case-Control Studies).

Study	Study Design	OR ^a		RR ^b		OR		RR		OR		RR		Quality Score (%)
		Ever Use	OR ^a	Ever Use	RR ^b	Current Use	OR	Current Use	RR	Past Use	OR	Past Use	RR	
Long et al. (2010)	Case-control study	0.95 (0.67–1.34)												96
Rudolph et al. (2013)	Case-control study	0.74 (0.54–1.03)												94
Campbell et al. (2007)	Case-control study	0.77 (0.65–0.91)												88

^aOR = odds ratio (95 percent confidence interval).

^bRR = relative risk (95 percent confidence interval).

Table 14. Colorectal Cancer (Meta-analyses).

Study	Study Design	OR ^a		RR ^b		OR		RR		Cases	Controls	Quality Score (%)
		Ever Use		Ever Use		Current Use	Past Use	Current Use	Past Use			
Luan et al. (2015)	Meta-analysis ^c	0.82 (0.76–0.88)		0.86 ^d (0.80–0.91)						7,679	2,301,822	95
Bosetti et al. (2009)	Meta-analysis	0.81 ^e (0.72–0.91)								11,677	711,134	91
		0.81 ^f (0.72–0.92)		0.82 ^g (0.69–0.97)						7,960	16,041	
		0.82 ^h (0.69–0.97)		0.81 ^g (0.75–0.89)						3,717	695,093	

^aOR = odds ratio (95 percent confidence interval).

^bRR = relative risk (95 percent confidence interval).

^cMeta-analysis of twelve cohort studies and seventeen case-control studies.

^dCohort studies.

^eCase-control studies.

^fAll studies.

^gSeven cohort studies.

^hEleven case-control studies.

Table 15. Skin Cancer.

Study	Study Design	OR ^a		RR ^b		OR		RR		Cases	Controls	Quality Score (%)
		Ever Use		Ever Use		Current Use	Past Use	Current Use	Past Use			
Birch-Johansen et al. (2012) ^c	Cohort			1.09 ^d (0.97–1.24)						1,175	25,925	89
Leslie and Espey (2005) ^f	Review	0.95 (0.87–1.04)		0.98 ^e (0.61–1.57)						76	25,925	
		0.95 (0.87–1.05)										

^aOR = odds ratio (95 percent confidence interval).
^bRR = relative risk (95 percent confidence interval).
^cNonmelanoma skin cancers only.
^dBasal cell cancer.
^eSquamous cell cancer.
^fORs from two meta-analyses of melanoma reviewed.

Bladder Cancer

According to the SEER statistics (<https://seer.cancer.gov/statfacts/html/urinb.html>), it is estimated that there are about 708,000 people in the United States with bladder cancer of which about 138,000 are women. There will be about 81,000 new cases of bladder cancer in 2018, with most being in men (estimated about 16,000 new cases in women), with about 17,000 deaths (about 3,400 in women). The five-year survival for bladder cancer is 77 percent. The data for bladder cancer are shown in Table 19. While one case-control study showed a decreased risk, another case-control study and a large cohort study failed to show a significant effect. Thus, there does not appear to be convincing evidence of a decreased or increased risk of bladder cancer in users of OCs.

Gastric Cancer

According to the SEER statistics (<https://seer.cancer.gov/statfacts/html/stomach.html>), it is estimated that there are about 98,000 people with stomach (gastric) cancer in the United States of which about 34,000 are women. There will be about 26,000 new cases of gastric cancer in 2018 (about 9,000 in women), with about 11,000 deaths (about 3,700 women). The five-year survival for gastric cancer is 31 percent. The data for gastric cancer are shown in Table 20. Although one cohort study showed a decrease in the RR of gastric cancer with OCs (Wang et al. 2016), other studies did not. Thus, there does not appear to be an effect of OCs on the risk of gastric cancer.

Pancreatic Cancer

According to the SEER statistics (<https://seer.cancer.gov/statfacts/html/pancreas.html>), it is estimated that there are about 69,000 people in the United States with pancreatic cancer, including about 30,000 women. There will be about 55,000 new cases of pancreatic cancer in 2018 (about 24,000 women), with about 44,000 deaths (about 19,000 women). The five-year survival for pancreatic cancer is 9 percent. The data for pancreatic cancer are shown in Table 21. None of the studies show a significant increased risk with the ever use of OCs, and although one study showed an increased risk with over ten years of use (Zhang et al. 2010), others did not (Teras et al. 2005). Thus, there does not appear to be an effect of OCs on the risk of pancreatic cancer.

Table 16. Thyroid Cancer.

Study	Study Design	OR ^a		RR ^b		OR		RR		OR		RR		Quality Score (%)
		Ever Use		Ever Use		Current Use	Past Use	Current Use	Past Use	Current Use	Past Use	Current Use	Past Use	
Schonfeld et al. (2011)	Cohort			0.9 ^c (0.7–1.1)								312	187,553	95
				1.23 ^d (0.93–1.65)								66	32,023	
				0.7 ^e (0.46–1.06)								26	22,508	
				0.48 ^f (0.28–0.84)								14	17,255	
				1.15 ^c (0.79–1.68)								127	69,920	86
												293	354	94
														69
Braganza et al. (2014)	Cohort													
Truong et al. (2005)	Case control	1.1 (0.8–1.7)		0.94 (0.85–1.04)								1,906	1,290,035	68
Cao et al. (2015)	Meta-analysis ^g			0.96 ^h (0.86–1.07)										
				0.89 ⁱ (0.73–1.08)										
				0.84 ^k (0.73–0.97)										
				0.96 ^l (0.94–0.98)										
				0.89 (0.78–1.02)										
				0.93 ⁿ (0.81–1.07)										
Wu and Zhu (2015)	Meta-analysis ^j													
Wang et al. (2015)	Meta-analysis ^m													

^aOR = odds ratio (95 percent confidence interval).

^bRR = relative risk (95 percent confidence interval).

^cHazard ratios are shown.

^dOne to less than five years of use.

^eFive to nine years of use.

^fTen plus years of use.

^gTwenty-five studies, including thirteen cohort studies, ten population-based case-control studies, and two hospital-based case-control studies.

^hCohort studies (thirteen).

ⁱPopulation-based case-control studies.

^jMeta-analysis of nine prospective cohort studies.

^kLongest versus shortest duration of COC use.

^lAdjusted annual relative risk.

^mSix cohort studies and three case-control studies limited to papillary thyroid cancer.

ⁿCohort studies only.

Table 17. Lung Cancer.

Study	Study Design	OR ^a		RR ^b		OR		RR		Cases	Controls	Quality Score (%)
		Ever Use		Ever Use		Current Use	Past Use	Current Use	Past Use			
Baik et al. (2010)	Cohort			1.1 (0.99–1.22)						1,729	105,442	94
Schwartz et al. (2015)	Cohort study									2,467	158,388	90
	<5 Years of use	0.98 (0.87–1.10)										
	5–9 Years of use	1.05 (0.89–1.23)										
	10+ Years of use	0.98 (0.84–1.16)										
Patel et al. (2016)	Cohort study			0.98 (0.85–1.12)						1,044	128,907	79
Tan et al. (2015)	Cohort study			0.88 (0.69–1.12)						311	27,911	77
Elliott and Hannaford (2006)	Case-control study	1 (0.7–1.6)								162	486	94
Pesatori, Carugno, Consonni, Hung, et al. (2013)	Case-control studies	0.81 (0.68–0.97)								1,961	2,609	92
Pesatori, Carugno, Consonni, Caporaso, et al. (2013)	Case-control study	0.67 (0.45–1.00)								407	499	88
Meinhold et al. (2011)	Case-control study	1.24 (0.92–1.69)								430	611	85
Wu and Zhu (2015) ^c	Meta-analysis	0.91 (0.81–1.03)								8,833	568,361	91

^aOR = odds ratio (95 percent confidence interval).
^bRR = relative risk (95 percent confidence interval).
^cMeta-analysis of nine case-control studies and five cohort studies.

Table 18. Kidney Cancer.

Study	Study Design	OR ^a		RR ^b		OR		RR		Cases	Controls	Quality Score (%)
		Ever Use		Ever Use		Current Use	Past Use	Current Use	Past Use			
Lee, Hankinson, and Cho (2009)	Cohort			0.99 (0.75–1.32)						287	118,219	96
Karami et al. (2013)	Cohort ^c			0.87 (0.75–1.02)						792	283,160	95
	1–3/4 Years of use			0.96 (0.80–1.17)								
	4/5–9 Years of use			0.86 (0.68–1.09)								
	Over 10 years of use			0.72 (0.55–0.96)								
Kabat et al. (2007)	Cohort study			0.8 (0.58–1.09)						172	89,617	82
	1–11 Months of use			0.81 (0.48–1.35)								
	12–35 Months of use			0.86 (0.53–1.40)								
	36–95 Months of use			0.75 (0.49–1.17)								
	96+ Months of use			0.8 (0.48–1.31)								
Zucchetto et al. (2008)	Case-control Study	0.91 (0.51–1.72)								273	546	88

^aOR = odds ratio (95 percent confidence interval).^bRR = relative risk (95 percent confidence interval).^cAnalysis of two cohort studies.**Table 19. Bladder Cancer.**

Study	Study Design	OR ^a		RR ^b		OR		RR		Cases	Controls	Quality Score (%)
		Ever Use		Ever Use		Current Use	Past Use	Current Use	Past Use			
Cantwell et al. (2006)	Cohort study			1.14 (0.77–1.70)						167	54,141	89
Dietrich et al. (2011)	Case-control study	1.55 (0.83–2.89)								207	364	91
Wolpert et al. (2010)	Case-control study	0.44 (0.29–0.65)								239	540	74

^aOR = odds ratio (95 percent confidence interval).^bRR = relative risk (95 percent confidence interval).

Table 20. Gastric Cancer.

Study	Study Design	OR ^a		RR ^b		OR		RR		OR		RR		Cases	Controls	Quality Score (%)
		Ever Use		Ever Use		Current Use		Current Use		Past Use		Past Use				
Wang et al. (2016)	Cohort study			0.67 (0.47–0.94)										269	33,753	89
Freedman et al. (2007)	Cohort study			1.05 (0.70–1.56)										154	73,288	81
Frise et al. (2006)	Case-control study	0.79 (0.43–1.45)		1.38 (0.56–3.38)										326	326	85
Camargo et al. (2012)	Meta-analysis			1.15 (0.71–1.88)												68

^aOR = odds ratio (95 percent confidence interval).
^bRR = relative risk (95 percent confidence interval).

Lynch Syndrome

Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer, is a genetic disease caused by alterations in genes involved in DNA mismatch repair. Lynch syndrome accounts for 3–5 percent of all cases of colorectal cancer (<https://www.cancer.net/cancer-types/lynch-syndrome>). The data for Lynch syndrome are shown in Table 22. One study evaluated endometrial cancer in patients with Lynch syndrome (Dashti et al. 2015), and similar to overall effects in endometrial cancer, they found a decreased incidence in ever users of OCs. Another paper looking at all extracolonic tumors also showed a decreased incidence in patients with the mutation, but interestingly showed a significant increase in mutation negative relatives (Blokhuys et al. 2010). Thus, in patients with Lynch syndrome, OCs appear to convey some protection against extracolonic cancers.

Multiple Cancers

Several papers examined multiple cancer types in single studies (Table 23). There were some papers that examined the incidence of all cancers in women exposed to steroidal contraceptives. One group looked at the incidence of all cancers in women using the levonorgestrel intrauterine-releasing system for heavy menstrual bleeding in Finland (Soini et al. 2014). They evaluated 108,077 women aged thirty to forty-nine at entry (1994) and ending in 2009 or aged fifty-five, or salpingectomy, oophorectomy, hysterectomy, or death. They found 3,235 cases of cancer, with an overall elevated risk of cancer (OR = 1.07; 95 percent CI [1.03, 1.11] for one or more purchase and OR = 1.2; 95 percent CI [1.09, 1.31] for two or more purchases) that was attributable primarily to an increase in breast cancer (OR = 1.19; 95 percent CI [1.13, 1.25] for one or more purchase and OR = 1.4; 95 percent CI [1.24, 1.57] for two or more purchases). No other tumor types had statistically significant findings. Another cohort study (Hannaford et al. 2007) examined the incidence of all cancers on combined steroidal contraceptives. They found an overall decreased risk (RR = 0.88; 95 percent CI [0.83, 0.94]), for ever use of OCs but did see an increased risk for use of ninety-seven months or more (RR = 1.22; 95 percent CI [1.07, 1.39]). Notably, this study was funded in part by several drug companies that sell OCs. One cohort study (Hannaford et al. 2007) evaluated all-cause mortality and cancer-related mortality in women on OCs. They found a decreased overall mortality (RR = 0.9; 95 percent CI [0.86, 0.95]) and cancer-

Table 21. Pancreatic Cancer.

Study	Study Design	OR ^a		RR ^b		OR		RR		Cases	Controls	Quality Score (%)
		Ever Use		Ever Use		Current Use	Past Use	Current Use	Past Use			
Teras et al. (2005)	Cohort study									1,959	386,022	90
	≤1 Year of use			0.93 (0.70–1.24)								
	2–5 Years of use			0.97 (0.75–1.25)								
	6–10 Years of use			0.92 (0.92–1.60)								
Navarro Silvera, Miller, and Rohan (2005)	11+ Years of use			1.3 (0.90–1.90)						187	89,645	88
	Cohort			1.09 (0.81–1.48)								
	Case-control study									323	117,841	85
	>0 to <1 year of use	1.1 (0.65–1.85)										
Zhang et al. (2010)	1 to <5 years of use	1.15 (0.78–1.68)										
	5 to <10 years of use	1.12 (0.74–1.69)										
	10+ years of use	1.72 (1.19–2.49)										
	Meta-analysis			1.09 (0.96–1.23)						7,873	2,396,141	92

^aOR = odds ratio (95 percent confidence interval).

^bRR = relative risk (95 percent confidence interval).

Table 22. Lynch Syndrome.

Study	Study Design	OR ^a		RR ^b		OR		RR		Cases	Controls	Quality Score (%)
		Ever Use		Ever Use		Current Use	Past Use	Current Use	Past Use			
Dashti et al. (2015)	Cohort study									133	995	89
Blokhuys et al. (2010) ^d	Case-control study	0.2 ^e (0.0–1.8)		0.35 ^c (0.20–0.63)						87	121	80
		3.7 ^f (1.3–10.9)										

^aOR = odds ratio (95 percent confidence interval).
^bRR = relative risk (95 percent confidence interval).
^cEndometrial cancer in patients with Lynch syndrome.
^dStudy of extracolonic cancer in patients with Lynch syndrome or their mutation negative relatives.
^eMutation positive patients.
^fMutation negative controls.

related mortality (RR = 0.91; 95 percent CI [0.85, 0.98]) in nonsmokers, but no significant effect in smokers (RR = 0.98; 95 percent CI [0.91, 1.05] for all-cause mortality and RR = 1.0; 95 percent CI [0.90, 1.12] for cancer-related mortality).

Discussion

The carcinogenicity of combined estrogen–progestogen contraceptives was evaluated by IARC working groups initially in 1998 (monograph published in 1999) and again in 2005 (monograph published in 2007). This was most recently updated with studies published through May 2008 (IARC 2012). Since that time, several important studies have been published, most of which are supportive of the IARC classification of OCs as Group 1 carcinogens and in agreement with the IARC evaluation of specific cancer types. In addition, several important studies have been published evaluating POCs and their cancer risk. In our evaluation here, we emphasized the most recent primary studies, giving greater weight to cohort studies which lack some of the intrinsic selection biases present in case-control studies. Meta-analyses are also noted but, as they typically include older studies, were given less weight as these had been reviewed by IARC previously.

In agreement with IARC, the recent data confirm an increased risk of breast cancer with the use of OCs (Table 1). This includes data from some very recent, large cohort studies (Mørch et al. 2017; Heikkinen et al. 2016; Poosari et al. 2014) with RRs ranging from 1.2 to 1.37. Since breast cancer is by far the most common cancer in women, affecting one in eight women, this translates into a substantial number of additional cancer cases. In addition, a large registry study of POCs (Soini et al. 2014, Table 22) showed an increased RR for breast cancer of 1.19. Increased duration of use also increases the risk of breast cancer for OCs as does use early in life (March 2017). The risk does decrease with increasing time since last use.

The IARC evaluation of an increased risk of cervical cancer with OCs is also supported especially by a large, high-quality cohort study (Roura et al. 2016; Table 4). This showed in particular a higher risk for invasive cervical cancer and a higher risk with current use. In contrast, the recent literature on liver cancer did not support an increased risk with OCs (Table 5). This discrepancy is likely accounted for by the observation by IARC that the increased risk for liver cancer was only apparent in populations with a low risk of hepatitis and chronic liver disease. These recent studies appeared to be in populations

Table 23. Multiple Cancer Types.

Study	Study Design	Tumor Type	OR ^a		RR ^b		OR		RR		Quality Score (%)	
			Ever Use		Ever Use		Past Use		Past Use			
Pfeiffer et al. (2013)	Cohort studies	Ovarian			1.36 ^c (1.17–1.59)					386	223	93
		Endometrial			1.44 ^c (1.29–1.62)					1,155	599	
Merritt et al. (2015)	Cohort	All-cause mortality, nonsmokers			0.9 (0.86–0.95)					Deaths	Total cohort	91
		All-cause mortality, smokers			0.98 (0.91–1.05)					14,383	322,972	
		Cancer mortality, nonsmokers			0.91 (0.85–0.98)							
		Cancer mortality, smokers			1.0 (0.90–1.12)							
Soini et al. (2016) ^d	Registry		1 or more		2 or more							88
		Population at risk →	93,843		14,234							
		All sites	1.07 (1.03–1.11)		1.2 (1.09–1.31)					2,781		
		Stomach	1.1 (0.80–1.47)		1.22 (0.49–2.51)					45		
		Colon and rectum	1.17 (0.99–1.36)		1.22 (0.78–1.81)					154		
		Liver	0.69 (0.25–1.50)		1.58 (0.19–5.69)					6		
		Gallbladder, bile ducts	0.88 (0.35–1.81)		1.77 (0.21–6.37)					7		
		Pancreas	0.5 (0.28–0.81)		0.66 (0.14–1.91)					15		
		Lung, trachea	0.68 (0.49–0.91)		0.31 (0.06–0.91)					43		
		Melanoma of skin	1.08 (0.90–1.27)		1.11 (0.67–1.73)					129		
		Breast	1.19 (1.13–1.25)		1.4 (1.24–1.57)					1,542		
		Cervix uteri	0.9 (0.69–1.15)		0.76 (0.28–1.65)					60		
		Adenocarcinoma of cervix uteri	1.18 (0.74–1.79)		0.91 (0.11–3.30)					22		
		Vulva	0.81 (0.35–1.59)		2.13 (0.44–6.21)					8		
		Vagina	1.32 (0.36–3.38)		0 (0.00–7.40)					4		
		Corpus uteri (all types)	0.59 (0.45–0.77)		0.36 (0.12–0.83)					56		
		Endometrial adenocarcinoma	0.46 (0.33–0.64)		0.25 (0.05–0.73)					37		
		Uterine sarcomas	1.44 (0.86–2.28)		1.17 (0.14–4.22)					18		
		Other uterine	0 (0.00–3.27)		0 (0.00–35.65)					0		
		Ovary, all types	0.6 (0.45–0.76)		0.51 (0.20–1.04)					59		
		Mucinous	0.43 (0.19–0.85)		0 (0.00–1.51)					8		
		cystadenocarcinoma ovari										
		Kidney	0.98 (0.70–1.32)		1.63 (0.78–3.00)					40		
		Bladder, ureter, urethra	0.98 (0.51–1.70)		1.75 (0.36–5.10)					12		
		Brain, nervous system	1.04 (0.89–1.19)		1.07 (0.69–1.57)					175		
		Thyroid gland	1.09 (0.92–1.28)		1.25 (0.77–1.90)					138		
		Non-Hodgkin's lymphoma	1.07 (0.85–1.32)		0.91 (0.44–1.67)					81		

(continued)

Table 23. (continued)

Study	Study Design	Tumor Type	OR ^a		RR ^b		OR		RR		Cases	Controls	Quality Score (%)
			Ever Use		Ever Use		Past Use		Past Use				
Hannafoord et al. (2007) ^e	Cohort	Hodgkin lymphoma	1.19 (0.63–2.03)		1.77 (0.21–6.41)						13		78
		Multiple myeloma	0.94 (0.47–1.68)		1.19 (0.14–4.29)						11		
		Leukemia	0.93 (0.64–1.29)		0.38 (0.05–1.37)						34		
		Ovarian borderline tumor	0.76 (0.54–1.03)		0.71 (0.23–1.65)						40		
					Ever use				≥97 months of use				
		Large bowel or rectum			0.72 (0.58–0.90)				0.95 (0.59–1.54)		323		
		Gallbladder or liver			0.55 (0.26–1.17)				1.52 (0.38–6.07)		27		
		Lung			1.05 (0.82–1.35)				1.35 (0.83–2.19)		297		
		Melanoma			0.92 (0.65–1.29)				1.71 (0.96–3.06)		146		
		Breast			0.98 (0.87–1.10)				1.22 (0.97–1.52)		1,339		
		Invasive cervix			1.33 (0.92–1.94)				2.73 (1.61–4.61)		154		
		Uterine body			0.58 (0.42–0.79)				0.57 (0.27–1.19)		156		
		Ovary			0.54 (0.40–0.71)				0.38 (0.16–0.88)		189		
		Central nervous system or pituitary			1.34 (0.73–2.47)				5.51 (1.38–22.1)		49		
Iodice et al. (2010)	Meta-analysis	Site unknown			0.64 (0.43–0.95)				1.16 (0.57–2.36)		99		81
		Other cancers			0.88 (0.79–0.98)				1.14 (0.91–1.44)		1,367		
		Main gynecological			0.71 (0.60–0.85)				1.11 (0.78–1.59)		499		
		Any cancer			0.88 (0.83–0.94)				1.22 (1.07–1.39)		3,877	43,296	
		Ovarian			0.5 ^f (0.33–0.75)						1,503	6,315	
		Breast			1.13 ^f (0.88–1.45)								
		Breast			1.05 (0.84–1.31)						558	64,411	
		Uterine body			0.89 (0.54–1.47)						119	64,411	
		Ovary			1.1 (0.66–1.84)						94	64,411	
		Thyroid			1.05 (0.60–1.82)						83	64,411	
Dorigochoo et al. (2009)	Cohort	Colon			1.24 (0.87–1.78)						207	64,411	75
		Rectum			1.16 (0.75–1.80)						136	64,411	
		Liver			0.99 (0.59–1.67)						95	64,411	
		Gallbladder hazard ratio			2.38 (1.26–4.49)						54	64,411	
		Pancreas			0.83 (0.45–1.55)						78	64,411	
		Stomach			0.83 (0.55–1.26)						168	64,411	
		Lung			1.03 (0.72–1.47)						229	64,411	
		Breast									235	235	
					3.72 (1.84–5.11)								
		Cervical			2.11 (1.44–3.08)						128	128	

(continued)

Table 23. (continued)

Study	Study Design	Tumor Type	OR ^a		RR ^b		OR		RR		Quality Score (%)
			Ever Use		Ever Use		Past Use		Past Use		
Vessey and Painter (2006)	Cohort	Ovarian			0.3 (0.1–0.5)				106	14,828	57
		Cervical			6.1 (2.5–17.9)				59	14,828	
		Uterine			0.1 (0.0–0.4)				77	14,828	
Vessey and Yeates (2013) ^g	Cohort	Ovarian			0.5 (0.4–0.7)						57
		Cervical			3.4 (1.6–8.9)						
		Uterine			0.5 (0.3–0.7)						
Friebel et al. (2014, June)	Meta-analysis	Breast	0.78 ^h (0.59–1.04)		1.59 ⁱ (1.32–1.92)						88
		Breast	1.04 ⁱ (0.81–1.32)		1.85 ^k (1.30–2.64)						
		Ovarian	0.40, 0.48, 0.56, 0.84 ^l		0.52 ^m						
		Ovarian	0.35, 0.39 ⁿ		1.04 ^o						
Moorman et al. (2013)	Meta-analysis	Ovarian	0.58 ^p (0.46–0.73)								87
		Breast	1.21 ^p (0.93–1.58)								

^aOR = odds ratio (95 percent confidence interval).

^bRR = relative risk (95 percent confidence interval).

^cStudy limited to women aged fifty years or older. RR is shown for the risk of *not* using COCs for at least one year.

^dStudy of women using the levonorgestrel intrauterine-releasing system for heavy menstrual bleeding. The control group was the age matched Finnish total female population. They evaluated those with one or more purchase or two or more purchases of the levonorgestrel intrauterine-releasing system.

^eNote that this study was funded in part by Schering AG, Schering Health Care, Wyeth Ayerst International, Ortho Cilag, and Searle and had a very high dropout rate.

^fMeta-analysis of eighteen studies, limited to BRCA1+ or BRCA2+ patients.

^gAdditional follow-up on the Vessey and Painter (2006) paper.

^hBRCA1 carriers, case-control studies.

ⁱBRCA1 carriers, cohort studies; hazard ratio are shown.

^jBRCA2 carriers, case-control studies.

^kBRCA2 carriers, cohort studies; hazard ratio are shown.

^lBRCA1 carriers, no meta-analysis performed, hazard ratios are shown.

^mBRCA1 carriers, no meta-analysis performed.

ⁿBRCA2 carriers, no meta-analysis performed, hazard ratios are shown.

^oBRCA2 carriers, no meta-analysis performed.

^pBRCA1 or BRCA2 carriers.

where hepatitis and chronic liver disease are endemic. This likely masked the effect of the OCs. Thus, there does not appear to be sufficient new evidence to overturn IARC's findings of an increased risk of liver cancer with OCs in populations where hepatitis and chronic liver disease are not endemic.

Several cancers were noted by IARC to have a lower risk with the use of OCs. This includes endometrial cancer (Table 6), ovarian cancer (Table 9), and colorectal cancer (Table 12). The IARC findings on endometrial cancer and ovarian cancer are supported by the recent studies reviewed. All the recent cohort studies of endometrial cancer show a reduced risk with OC use, and the risk further decreases with longer use with an annualized RR estimated as 0.95 (Hüsing et al. 2016). Similarly, for ovarian cancer, risk is reduced with OCs, and this further decreases with longer use with an annualized RR estimated as 0.94 (Gay et al. 2015). The relatively low frequency of these cancers in comparison to breast cancer would suggest that the overall cancer risk for women would still be increased by OCs.

One discrepancy between recent studies and the IARC review is regarding colorectal cancer (Table 12). The most recent IARC monograph notes that an inverse relationship has been established between exposure to OCs and colorectal cancer. However, since that publication, several high-quality cohort studies have been published, which do not support a significant effect (Tsilidis et al. 2010; Zervoudakis et al. 2011; Charlton et al. 2015; Brändstedt et al. 2014). One study evaluating anal cancer showed an increased RR with OC use (Coffey et al. 2015). This suggests that the risk profile for colorectal cancer with the use of OCs may be changing with newer preparations. IARC should examine this more recent data and consider revising the findings with regard to colorectal cancer.

No other cancer type was found in these analyses to have an increased or decreased risk of developing with the use of OCs. There were a few papers that evaluated overall cancer risk. One looked at a POC, specifically evaluating the levonorgestrel intrauterine-releasing system for heavy menstrual bleeding (Soini et al. 2014; Table 22). They found an overall RR for the development of any cancer of 1.07 with one or more prescription and 1.2 with 2 or more prescriptions. This was almost entirely from the increase in breast cancer risk (RR = 1.19 with one or more prescription and RR = 1.4 with two or more prescriptions). Similar to OCs, they saw a decrease in the risk of endometrial and ovarian cancer (RR of 0.46 and 0.6, respectively, with one or more use). In contrast, a similar study of OCs

(Hannaford et al. 2007) showed an overall significantly decreased risk for all cancers (RR = 0.88) but oddly showed a significantly increased RR with the past use of OCs (RR = 1.22). This study suffered from a very high dropout rate, making the results suspect. It was also funded by several pharmaceutical companies who sell OCs and POCs.

There are also moral implications from these findings. As noted by Blessed Pope Paul VI (1968), contraceptives separate the unitive and procreative aspects of the marital act with many negative predicted consequences. OCs and POCs suffer from an additional moral problem: They treat a normal functioning body system (the female reproductive system) as if it were a disease. Potent steroids have a profound effect on the physiology of multiple cells, tissues, and organs in the female body. These extend beyond inhibiting ovulation and thinning the endometrium. OCs and POCs work on other epithelial cells, especially in the mammary glands and cervix, to increase their proliferation. With each cell division, there is a chance for mutation, which increases the risk of carcinogenesis. While the scientific basis for OCs and POCs acting as Group 1 carcinogens may be apparent, the moral aspect may be less so. Because of the profound unity of body, mind, and spirit of the human person, things that affect one will affect the others. Thus, spiritual insults to the person (i.e., sins) will invariably have sociological, psychological, and physical consequences. Contraception in and of itself disrupts the most fundamental of human interactions: the marital act. Contraception attempts to separate the unitive and procreative aspects of the marital act. It logically follows that human interactions will be directly affected. Indeed, a variety of sociological consequences have been attributed to the use of contraception (e.g., increased divorce rates, the use of women as objects, a coarsening of morality). Steroidal contraceptives also suffer from the moral evil of treating fertility as a disease. This is against the integrity of the human person and the ethical principle of respect for persons, not to mention the imperative to do no harm (i.e., inhibiting the normal functioning of a bodily system). It therefore logically follows that physical harm may come to women. This is seen in the many, common side effects of OCs and POCs, which are detailed in the individual prescribing information. Increases in several types of cancer are some of the most serious consequences of OC/POC use.

In our society today, there are many effective, natural alternatives to the use of OCs and POCs. Physicians are morally obligated to treat the whole patient as well as to do no harm. Promoting the use

of natural methods of family planning and fertility awareness and discouraging the use of carcinogenic OCs and POCs more effectively diminish harm and respect the integrity of the patient as a human person.

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Note

1. Not used for meta-analyses.

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