A MINI-REVIEW OF EFFECT OF ORAL CONTRACEPTIVE PILLS ON THE RISK OF BREAST CANCER AMONG FEMALES: A META-ANALYSIS FROM 27 OBSERVATIONAL STUDIES

ENAS AL-KHAFAJI [*] AND DANIA KABBANI

Department of Pharmaceutical Sciences, Faculty of Pharmacy, University of Jordan, Amman, Jordan

***Corresponding Author: E Mail: alkhafajienas@gmail.com**

ABSTRACT

Breast cancer is the most common malignancy among women in the United States. The association between the use of oral contraceptives pills (OCPs) among females and the risk of breast cancer has been a long-standing concern, where many studies showed conflicting results. To investigate the association between use of OCPs and the subsequent risk of breast cancer, individual participant data from 27 observational studies of the effect of OCPs on breast cancer have been brought together and analyzed centrally.

Key word: Breast cancer, Meta-analysis, Forest plot, Oral Contraceptive, Users, Non users, High risk, Low risk

1. INTRODUCTION

Breast cancer is the most common malignancy among women in the United States (14). The association between the use of oral contraceptives pills (OCPs) among females and the risk of breast cancer has been a long-standing concern, where many studies showed conflicting results (3). To investigate the association between use of OCPs and the subsequent risk of breast cancer, individual participant data from 27 observational studies of the effect of OCPs on breast cancer have been brought together and analyzed centrally.

Our aim in this report is to the see if there is relationship between Oral Contraceptive use and the risk of breast cancer in women. We conducted a literature search updated to on the following databases: Pubmed, Science

direct, Medline, and Journal of cancer and Cochrane library.

2. MATERIALS AND METHODS

2.1. Literature review and collection of the relevant studies

We searched the following databases: Pubmed, Science direct, Medline, and Journal of cancer, and Cochrane library to identify studies of the effect of OCPs on breast cancer published in or after 1980. Search terms used included breast neoplasms, breast cancer, oral contraceptives, oral contraceptive pills, contraceptive agents, case-control studies, and cohort studies. Thirty-five studies were identified among which only 27 studies were found to meet the inclusion criteria [the study have both control (OCPs non-users) and cases (OCPs user for ≥ 8 years) groups]. Sixteen studies were cohort prospective studies and eleven was case-control retrospective studies. Studies were excluded because most women had used OCs for 6 months or less (one study), and females have a gene mutation for breast cancer (7 studies). Thus, there were a total of 27 potential independent studies for analysis, which are listed in **Table 1**. From those studies, two reviewers extracted the required data (sample size for each group, relative risk (RR), 95% confidence interval (CI) of the RR).

2.2 Statistical analysis

1-Statistical analyses using Microsoft Excel 2010 (FOREST calculation) was performed in order to calculate the pooled RR of breast cancer in relation to the use of OCPs and their corresponding 95% CI using data from the 27 selected observational studies.

2-The pooled RR of breast cancer per ≥ 8 years duration of oral contraceptive use was estimated following log-transformation of the RR and 95% CI.

3-Following that the log standard error (SE) was calculated using the following equation:

$$\text{Log upper limit 95\% CI} = \log RR + 1.96 * \log SE$$

From the log SE the weight (w) of each study was calculated using the following formula:

$$w = 1/(\log SE)^2$$

The studies with higher SE will have smaller w within the final pooled RR.

The log RR for each study was multiplied by the weight of that study and the final sum was divided by the total w of all studies to calculate the log of the pooled RR which was then transformed to the pooled RR (antilog value).

From the total w, the log pooled SE was calculated by taking the square root of the reciprocal of the w as following:

$$\text{Log pooled SE} = (1/w)^{1/2}$$

Finally, antilog transformation was used to calculate the pooled SE, from which the 95% CI of the whole studies was calculated.

country, duration of OCPs use, age of participants, and the relative statistical data (sample size, RR, and 95% CI of the RR).

3. RESULTS

Table 1 represents the details of the selected 27 observational studies. The studies contain details about authors names, study design,

Result of Meta-analysis and forest plot was shown in **Figures 1 and 2** respectively for all studies recorded.

Study	RR	ULCI	LOG RR	LOG ULCI	SE	w	w* log RR			
1	1.42	1.94	0.15229	0.2878	0.069139482	209.193	31.8577			
2	1.3	1.5	0.11394	0.17609	0.031708116	994.624	113.331			
3	1.29	1.6	0.11059	0.20412	0.047719527	439.145	48.5649			
4	1.4	1.79	0.14613	0.25285	0.054451528	337.272	49.2848			
5	0.98	1.1	-0.00877	0.04139	0.025595209	1526.45	-13.393			
6	1.11	1.32	0.04532	0.12057	0.038393343	678.404	30.7473			
7	0.7	0.8	-0.1549	-0.09691	0.029587728	1142.29	-176.943			
8	0.8	1.44	-0.09691	0.15836	0.130241074	58.9527	-5.71311			
9	0.9	1.5	-0.04576	0.17609	0.113188138	78.0545	-3.57158			
10	1	1.8	0	0.25527	0.130241074	58.9527	0			
11	1.05	1.31	0.02119	0.11727	0.049021427	416.129	8.81748			
12	1.31	1.79	0.11727	0.25285	0.069174355	208.982	24.5076			
13	1.35	2.78	0.13033	0.44404	0.160056647	39.0349	5.08756			
14	1.01	1.11	0.00432	0.04532	0.020919186	2285.13	9.87489			
15	1.2	1.4	0.07918	0.14613	0.034156525	857.142	67.8695			
16	1.69	2.69	0.22789	0.42975	0.102992641	94.2731	21.4836			
17	0.77	1.12	-0.11351	0.04922	0.083024131	145.075	-16.4673			
18	1.47	1.87	0.16732	0.27184	0.05332871	351.623	58.8327			
19	1.31	2.5	0.11727	0.39794	0.143198323	48.7668	5.71894			
20	1.3	1.7	0.11394	0.23045	0.059441617	283.021	32.2484			
21	1.06	2.05	0.02531	0.31175	0.146146937	46.8188	1.18479			
22	1.18	1.87	0.07188	0.27184	0.102020204	96.0788	6.90634			
23	2.6	5.4	0.41497	0.73239	0.16194919	38.1279	15.822			
24	1	1.2	0	0.07918	0.040398595	612.728	0			
25	1.3	1.5	0.11394	0.17609	0.031708116	994.624	113.331			
26	1	1.4	0	0.14613	0.07455512	179.906	0			
27	1.3	3.1	0.11394	0.49136	0.192560378	26.9691	3.07295			
Total						12247.8	432.455			
						Log RR	0.03531	RR		1.08469815
						SE	0.00904	UL		1.10240852
								LL		1.06698778

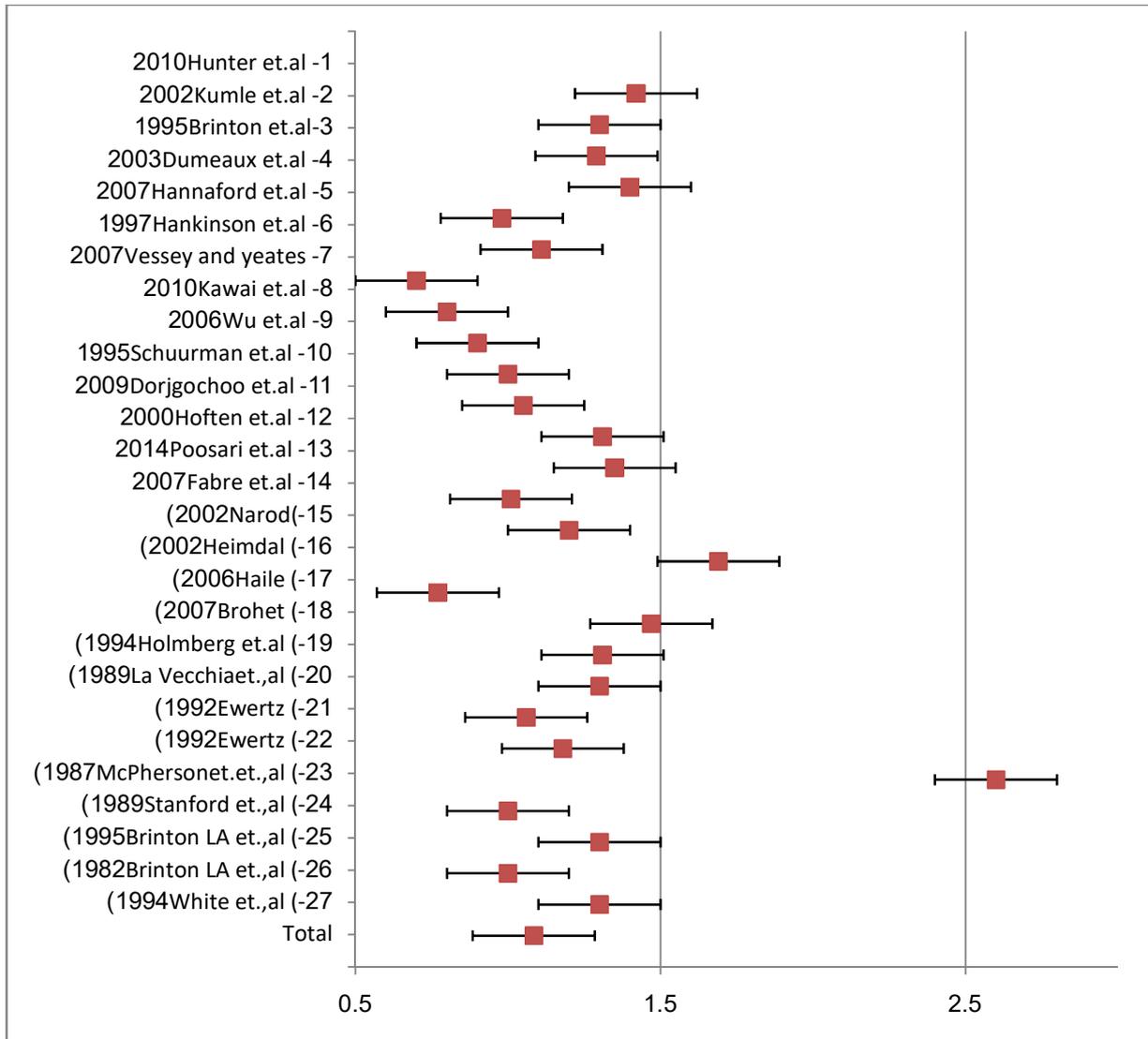**Figure 1: Meta-analysis conducted on all studies recorded**

Figure 2: Forest plot

Table 1: Details of studies and characteristics of females includes

Study	Type of study	Country	Duration of OCP use	Age of female participants	No. cases	No. control	Total sample	RR	95% CI
Hunter et.al (2010)[1]	cohort	Boston	≥8 years	24-43 years	98	162	260	1.42	(1.05-1.94)
Kumle et.al (2002)[2]	cohort	Norway	≥10 years	30-49	18876	28171	47047	1.3	(1-1.5)
Brinton et.al (1995)[3]	cohort	USA	≥10 years	20-45	N.A	N.A	234	1.29	(1-1.6)
Dumeaux et.al (2003)[4]	cohort	Norway	≥10 years	30-70	86	305	391	1.4	(1.09-1.79)
Hannaford et.al (2007)[5]	cohort	U.K	≥10 years	<59	891	448	1339	0.98	(0.87-1.1)
Hankinson et.al (1997)[6]	cohort	USA	≥10 years	30-55	4142	62137	66258	1.11	(0.93-1.32)
Vessey and yeates (2007)[7]	cohort	U.K	≥10 years	35-44	112	658	770	0.7	(0.5-0.8)
Kawai et.al (2010)[8]	cohort	Japan,	≥10 years	40 – 60	285	23779	24064	0.80	(0.45 – 1.44)
Wu et.al (2006)[9]	cohort	China	≥10 years	30 – 64	104	11785	11889	0.9	(0.6 – 1.5)
Schuurman et.al (1995)[10]	cohort	Netherland	10 – 14 years	55 – 69	471	62102	62573	1.0	(0.6 – 1.8)
Dorjgochoo et.al (2009)[11]	cohort	China	≥10 years	40 – 70	558	66103	66661	1.05	(0.84 – 1.31)
Hoften et.al (2000)[12]	cohort	Netherland	≥10years	42 – 63	399	11785	12184	1.31	(0.96 – 1.79)
Poosari et.al (2014)[13]	cohort	Thailand	≥10 years	30 - 69	9261	2153	11 414	1.35	(0.65–2.78)
Fabre et.al (2007)[14]	cohort	Roussy	9 years	50	2390	71274	73 664	1.01	(0.93-1.11)
Narod (2002)[15]	cohort	Multicenter	≥10 years	Mean age=47	1230	2647		1.2	(1.02-1.4)
Heimdal (2002)[16]	Case Control	Norway	10–14 years	Mean age=42	106	1317	1423	1.69	(1.06, 2.69)
Haile (2006)[17]	Case Control	Multicenter	≥10 years	Mean age < 50	312	578		0.77	(0.53–1.12)
Brohet (2007)[18]	Retrospective cohort	Multicenter	Any duration of use	Mean age=41	258	300		1.47	(1.16–1.87)
Holmberg et.al (1994)[19]	Case Control	Sweden and Norway	8-11 (years)	Different age group	51	96	422	1.31	(0.6-2.50)
La Vecchia et.,al (1989)[20]	Case Control	Italy	2 -10 years	Below 60 year	1517	1351	2868	1.3	(1.0–1.7)
Ewertz (1992)[21]	Case Control	Denmark	8-11 years	Below 40 year	203	212	415	1.06	(0.55-2.05)
Ewertz (1992)[22]	Case Control	Denmark	≥10 years	(40-59) years	856	779	1635	1.18	(0.75-1.87)
McPherson et.,al (1987)[23]	Case Control	London	4 years	Mean age =45 years	351	351	351 pairs	2.6	(1.3-5.4)
Stanford et.,al (1989)[24]	Case Control	USA	Ever use		2,022	2,183	4205	1	(0.9-1.2)
Brinton LA et.,al (1995)[25]	Case Control	USA	> 10 years	Younger than 45 years	2203	2571	4774	1.3	(1.1-1.5)
Brinton LA et.,al (1982)[26]	Case Control	USA	Ever used	Younger than 40 years(Premenopausal)	224	189	413	1.0	(0.8-1.4)
White et.,al (1994)[27]	Case Control	western WashingtnState	>10 years	21-45	747	961	1663	1.3	(0.9-3.1)
Total	------	------	------	-----	47735	349182	396917	1.08	(1.06-1.10)

4. DISCUSSION

Over all 396917 females were included in all of the studies, from which 349182represent the control group (OCPs non-users) and 47735 represent the cases (OCPs users). From **Table 1** it was evident that the RR for OCPs use of ≥ 8 years was **1.08**(95% CI **1.06-1.10**). Where is using OCPs ≥ 8 years is associated with 8% significant increase in the risk of breast cancer compared to non-users.

5. CONCLUSION

Use of OCPs was associated with significant increase of breast cancers risk among female's users of ≥ 8 years duration.

5. ACKNOWLEDGMENT

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