

Table 1: Summary of breast cancer risk studies in infertile women

HR = Hazard Ratio; RR = Relative Risk; SIR = Standardized Incidence Ratio

Author	Location	Study Population	Sample	Results/Findings	Follow-Up	Key Limitations
Brinton et al, 2014	NA	9,892	Evaluated for infertility	749 with breast cancer	Median 30 years	
			38.10% who took clomiphene	Somewhat elevated risk (HR=1.05)		
			High clomiphene use and >6 cycles	Statistically significant elevated risk (HR=1.27)		
			9.6% who took gonadotropins (usually in combination with clomiphene)	Risk increased significantly only in women who remained nulligravid.		
Lerner-Geva et al, 2006	Israel	5,788	Attended infertility clinic 1964-1984	131 cases of breast cancer with mean age at diagnosis 47.2 years. Compared to general population, SIR was not significantly increased.	20 years; Mean follow-up after 1st visit 20.9+6.6 years; Mean time between 1st visit and breast diagnosis, 19 years.	Women who were deceased, some from cancer, were not included.
				Subgroup analysis - clomiphene significantly increased risk of breast cancer (SIR=1.4) compared with unexposed women.		
Calderon-Margalit et al, 2008	Israel	15,030	Parous women gave birth in 1974-1976 and 567 used drugs to induce ovulation	Significantly increased breast cancer risk HR=1.65. Significantly increased overall cancer risk, HR=1.36. Median age of breast cancer diagnosis 49.4 (lower than general population).	Median 29 years	
				Those who waited 12 months to conceive		
Stewart et al, 2012	Australia	21,025	Age 20-44 seeking treatment 1983-2002	384 cases of breast cancer (236 did not have IVF and 148 did); Mean age for those who did not have IVF was 46.4 and those who did 47.1.	Mean 16 years	
				Woman who had IVF at young age (about 24)		

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Li et al, 2012 Meta-analysis	NA	746,455	Participants from 8 cohorts, 7 of which included examination of breast cancer risk. General population used as control in 5 of the 7 studies. Women who had live births used as control in 2 of the 7 studies.	No overall increase in cancer risk, significant increase in ovarian cancer risk, and no increase in breast cancer risk.	Largest group (Kristiansson et al, 2007) had a mean f/u of 6.2 years for 89.8% of total cohort.	Follow-up was too short, only 3.6-10 years.
Sergentanis et al, 2016 Meta-analysis	NA	1,554,332	Included 5 of the same studies as Li et al but added 3 more recent studies.	14,961 cases of breast cancer, including 576 among woman exposed to IVF. No significant increase in breast cancer compared to general population or infertile women.	Largest group (Kallen et al, 2011), mean follow-up was 8.3 years for 89% of total cohort.	Follow-up was too short. Only 1 of the 8 studies (Stewart,[2012]) had more than 8.3 years.