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The risk of breast cancer with progestin only contraceptive methods.

Use of combined oral contraceptives, containing both estrogen and progestogen, has previously been associated with a small increase in breast cancer risk among current and recent users in prospective and epidemiological studies, but there has been limited data about the effect of progestogen-only hormonal contraceptives.

A study published in March 2023 in the open access journal *PLOS Medicine* by Fitzpatrick and colleagues reported a relative increase of 20% to 30% in breast cancer risk associated with both combined and progesterone-only contraceptives, whatever the mode of delivery, though with five years of use, the 15-year absolute excess incidence is at most 265 cases per 100,000 users.

With five years use of either oral combined or progestogen-only contraceptives, the associated 15-year absolute excess incidence of breast cancer was estimated at 8 cases per 100,000 hormonal contraceptive users at age 16-20 years and 265 cases per 100,000 users at age 35-39 years. The odds of breast cancer were similarly and significantly raised, regardless of whether the contraceptive used was a combined (estrogen and progestogen) oral preparation (OR=1.23 95%CI 1.14-1.32, p<0.001), a progestogen-only oral preparation (OR= 1.26 95% CI 1.16-1.37, p<0.001), an injected progestogen (OR= 1.25 95% CI 1.07-1.45, p=0.004), or a progestogen releasing intra-uterine device (OR=1.32 95% CI 1.17-1.49, p<0.001).

A Swedish cohort study using nationwide registers included women aged 15-34 in 2005 and those that turned 15 thereafter, until the end of 2017 or age 45. During 172,132 person years of progestogen-only pill use (any type), 78 breast cancers occurred. Compared to individuals that did not use hormonal contraception during the study period, current users of a progestogen-only pill (any type) had an adjusted relative risk of incident breast cancer (invasive or in situ) of 1.40 (95% CI 1.26-1.56; p<0.01). Adjustment was made for age, education, place of birth, parity, age at first term pregnancy, and adjustment for BMI could be made for some women who had given birth. It could not adjust for smoking and alcohol. Relative risk appeared to be highest during the first 10 years of use of progestogen-only contraception (RR 1.74 (95% CI 1.44-2.10) at 1-5 years and RR 1.26 (95% CI 1.06-1.49) at 5-10 years and to be no longer apparent 10 years after stopping. The study also found an increased risk for breast cancer with LNG-IUS use at 1.21 (95% CI 1.01-1.33)

Similar results were reported earlier in a Danish study with an increased risk for any hormonal contraceptives. Women who currently or recently used the LNG- intrauterine system had a higher risk of breast cancer than women who had never used hormonal contraceptives (relative risk, 1.21; 95% CI, 1.11 to 1.33). The overall absolute increase in breast cancers diagnosed among current and recent users of any hormonal contraceptive was 13 (95% CI, 10 to 16) per 100,000 person-years, or approximately 1 extra breast cancer for every 7690 women using hormonal contraception for 1 year (Mørch et al.2017).

Based on biological effects the slightly increased risk for breast cancer in hormonal contraceptive users may not be surprising as progestogen is mitogenic in breast. Although estrogen exerts proliferative effects on mammary epithelial ducts directly via estrogen receptors (Mallepell et al, 2006), it also upregulates the expression of the progesterone receptor (Daniel et al, 2011). Furthermore, in menopause progestogen addition to estrogen in MHT increases risk over estrogen alone.

A new Danish study (Mørch et al 2024) investigated the association of all available LNG-IUS on risk of breast cancer using Danish national registers. Risk was adjusted for age, calendar period, duration of previous hormonal contraception use, fertility drugs, parity, age at first birth ,polycystic ovarian syndrome, endometriosis, and highest achieved educational level. As for any epidemiological study, risk could not be fully adjusted for BMI nor alcohol use. The hazard ratio (HR) for breast cancer was1.4 (95%CI, 1.2-1.5) with LNG-IUS use compared with to no use of hormonal contraceptives. Authors could not see a significant influence on duration of use on the risk. (P=.15). Thus- this study confirms results of previous studies that use of progestin for contraception infers a slightly increased risk for breast cancer.

These small excess risks must, however, be viewed in the context of the well-established benefits of hormonal contraceptives and especially LARC use. These benefits include a high contraceptive efficacy, lower risk of endometrial cancer and reduced menstrual flow, treatment of heavy menstrual bleeding and dysmenorrhea and treatment of endometriosis. Women above 40 years have a higher risk of developing heavy menstrual bleeding. It can be concluded that the possible increased risk for breast cancer is small and even less than that for other risk factors such as lifestyle factors and especially overweight. The new data has not changed the risk-benefit- balance or the recommendations on contraceptive use.

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