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Endometrial Cancer with Progestin and Estrogen Oral Contraceptives and Hormone Therapy – A Review and Analysis of the Current Data

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Introduction

Epidemiological studies reveal a variety of mostly hormone-related risk factors for endometrial cancer. These include obesity, early menarche and late menopause, nulliparity, polycystic ovaries, diabetes, being postmenopausal, older age, hormone therapy for breast cancer, and, an inherited colon cancer syndrome. The incidence of endometrial cancer in the US was 25.4 cases/100,000 women per year from 2009 to 2013 with 4.5/100,000 deaths per year and a 5 year survival rate of 81.7% (SEER Stat Facts).

Many epidemiological studies have claimed that progestin and estrogen oral contraceptives (OCs) prevent endometrial cancer but estrogens given alone caused a large epidemic of endometrial cancer in the United States from the mid1960s to a peak in 1975 with longer use increasing the risk 22 times [1,2]. Also progestins and estrogens increased the risk of endometrial cancer if used as menopausal hormones in normal weight women [3]. Why is there epidemiological confusion?

In 2015 the Collaborative Group on Epidemiological Studies on Endometrial Cancer meta-analysed 36 epidemiological studies of OC use in women with an intact uterus [4]. The Group claimed that OC use prevented endometrial cancer with the risk ratio reducing by 0.76 every 5 years of use with more risk reduction for carcinomas than sarcomas. The 36 epidemiological studies, originally published between 1987 and 2013, included 27 276 cases of endometrial cancer diagnosed at a mean age of 63 years (IQR 57-68) with a median year of cancer diagnosis of 2001. The Group's interpretation was that OC use conferred long-term protection and about 400,000 cases of cancer before age 75 years had been prevented during the 50 years from 1965 to 2014, including 200,000 cases in the last decade. The Group's claim is questionable because 95% of OC use was in decades long past in the 1960s and 1970s. Web-supplementary table A2 listed OC usage for 37,982 controls and 7709 endometrial cancer cases but only 10.7% of ever user cases (824/7709) were current users or users of OCs less than 15 years previously whereas 89.3% of ever user cases (6885/7709) took OCs 15 to 30 years or more previously.

Women diagnosed at an average age of 63 years in 2001 were more likely to be current or recent users of menopausal hormones or breast cancer therapies than current users of hormonal contraceptives. Although 46% of cases and 42% of controls had used hormone therapy (HT) more recently, the carcinogenic effect of more recent HT or breast cancer therapy in OC ever users or never user controls was merely "stratified for". The Group did not prove that ever using OCs prevented 400.000 endometrial cancers as was widely reported. In fact, their list of registrations of endometrial cancers in 21 Western developed countries and from 1965 to 2014 showed that registrations increased by 48.3% overall in 40 to 75 year age groups from 485,325 to 719,750 cases but doubled in 30 to 39 year olds from 8,511 to 17,438 cases.

Grant asked the Group's 71 collaborating epidemiologists in a Lancet Oncology Correspondence a crucial, but so far unanswered, question, "How many women took hormones for any reason when, or near the time that, they developed endometrial cancer compared with an aged matched group of never ever users?" [5].

As with breast cancer, epidemiologists have been confused by the fact that endometrial cancer is more common in older than younger women. However, since the early 1960s increases in numbers of both breast and endometrial cancers have been greater in younger premenopausal or peri-menopausal women than older women because of exposures to progestin and estrogen use for both contraception and menopausal hormone therapy (HT). Progestins levonorgestrel and norgestrel, and also norethisterone (which has some inherent estrogenicity), are used in similar doses for either contraception or therapy. Medroxyprogesterone acetate (MPA) has been used in a long acting form for contraception or as daily pills for menopausal symptoms as in the prematurely terminated Women's Health Institute randomised double blind trial. The trial of MPA and conjugated estrogen HT in more than 27,000 women was stopped in July 2002, after 5.6 years, because of increases in breast cancer, venous thromboembolism, coronary heart disease (CAD) and stroke [6].

Similar or identical progestins have been used in similar doses for either contraception or hormone therapy. The Group stratified their relative risk estimates for "any type of menopausal hormone therapy". Progestins and estrogens are potentially carcinogenic whatever the reasons for use. In 2007 the International Agency for Research on Cancer classified contraceptive and menopausal progestagen-oestrogen combinations as Group 1 carcinogens particularly for breast, ovarian and cervical cancers [7].

An important confounding factor in epidemiological studies of endometrial cancer has been high hysterectomy rates in young women [8]. For example, in England and Wales in 1981 there were 34,590 hysterectomies compared with 119 endometrial cancer registrations in women under age 45 years. In 1980 The Walnut Creek Contraceptive Drug Study reported that users of OCs aged 18 to 39 years were more likely to have hysterectomies and also more reasons for hysterectomy including increases in cervical cancer, menstrual disorders, fibroids, anaemia due to blood loss, pelvic inflammatory disease, uterovaginal prolapse and adenomyosis [9].

By 1990 in England and Wales there were 73,280 hysterectomies registered in women under age 45 years. As many more hysterectomies were registered in young women than endometrial cancers, this must have prevented large numbers of OC users developing endometrial

cancer [8]. However, the introduction of endometrial ablation for menorrhagia in the early 1990s has been followed by a reduction in the number of hysterectomies [10]. Brewster commented that the decrease in rates of hysterectomy since the mid-1990s, noted in the USA, England and Scotland, could in the short-term result in fewer cancers being detected as incidental findings, following routine pathological assessment of resected specimens [11]. However, he wrote that in the longer term it leaves a larger population at risk of developing uterine cancer, and therefore may also be contributing to the increases in uterine cancer incidence reported by the UK cancer registries. Also up to 40% of the increase in endometrial cancer is being attributed to increasing levels of obesity. One of the main reasons for discontinuing use or progestins and estrogens is an increase in weight. In 2013 a US study of 30 etonorgestrel (ENG) implant users, 130 levonorgestrel intrauterine system (LNG-IUS) users, and 67 depot medroxyprogesterone acetate (DMPA) users, the mean weight change (in kilograms) over 12 months was 2.1 for ENG implant users; 1.0 for LNG-IUS users; and 2.2 for DMPA users [12].

Over 50 progestin and estrogen OC formulations were tested in London in the 1960s to find lowest tolerable doses preventing pregnancy and early discontinuation [13-17]. Effects varying with increasing progestagenic potency were breakthrough bleeding, venous dilatation and thromboembolism, endometrial arteriolar development and migraine headaches, weight gain, and, depressive mood changes with high endometrial monoamine oxidase activity. The result was that all OC's marketed have been predominantly progestagenic to prevent irregular bleeding and/or pregnancy. In addition, following the epidemic of estrogen-induced endometrial cancer, all HT combinations for women with a uterus also became predominantly progestagenic.

However, a 2010 study found longer use of estrogen, sequential, or, continuous progestin/estrogen HT in normal weight women, increased endometrial carcinomas [3]. As combined HT can increase the risk of endometrial cancer, past OC use is unlikely to be protective. Estrogen use stimulates hyperplasia and cancer of the endometrial glandular epithelium and progestin use induces endometrial atrophy with small sparse endothelial glands, but with high glandular monoamine oxidase activity and often increased arteriolar development, so an atrophic endometrium may be more likely to develop a carcinoma or sarcoma.

Progestins and estrogens use can lower zinc and raise copper levels which impair cellular superoxide dismutase activities and liver clearance of carcinogens [18]. Chan and Kotani found that in OC user's levels of derivatives of reactive oxygen metabolites, which they used to measure the overall oxidative stress burden by analysing the oxidation of various components such as lipids, proteins and nucleic acids, positively correlated with the level of C-reactive protein, a marker of chronic inflammation. They proposed that OC use might increase breast cancer by increasing inflammation [19]. Also Krintus and colleagues found that use of second and third generation OCs increased C-reactive protein levels [20].

Use of progestins and estrogens, whether used for contraception or menopausal therapy, can cause chronic inflammation with heightened oxidative stress and increase the risk of breast and other cancers including endometrial cancer, endometriosis and coronary artery disease [21]. It is unfortunate for women that the fact that use of progestins and estrogens can increase oxidative stress continues to be ignored with many potentially serious consequences.

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