HYPOTHESIS

RISK FOR MALIGNANT TUMORS AFTER ORAL CONTRACEPTIVE USE:
IS IT RELATED TO ORGAN SIZE WHILE TAKING THE PILL?

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(Received 12 June 1989; accepted 20 September 1989)

INTRODUCTION

Oral contraceptive use (OC-use) has previously been found to reduce the risk of cancer of the uterine corpus and ovary. This reduction in risk has not been seen for cancer of the breast. For certain subgroups, such as early users, users before the first full term pregnancy, and very long term users an increased risk for breast cancer has been found in some studies. Also, studies of cancer of the uterine cervix and the liver suggest that the risk may be higher after OC-use, even if control for potential confounders; such as infections (e.g. with human papilloma virus), and tobacco use in patients with cervical cancer, and hepatitis B-virus infection in patients with liver cancer may be difficult. In this paper the author would like to forward the hypothesis that the cancer risk for a particular organ after OC-use may be related to the size of that organ while taking the pill. The hypothesis is a proposal for continued research in this area and should not by itself be used as an argument for changing prescription habits of modern OCs prematurely.

EVIDENCE FOR THE HYPOTHESIS

There is a relationship between proliferation of the epithelium of an organ and its propensity for carcinogenesis. Further, the cell number may also relate to the risk that an organ experiences, especially if the proliferative cell number is considered.

One possible explanation for the finding that breast cancer in general is more common in the left breast than in the right breast is that the risk is related to breast size, as the left breast on the average is slightly larger than the right breast.

Breast size may also be of importance for the lower risk of breast cancer in men and the lower risk in oriental women compared with caucasian women.

The breast and uterine cervix develop their maximal size (as non-pregnant) early in reproductive life. It is also believed that the propensity for carcinogenesis is especially high during the same time period for the two organs.

OC-use does not decrease the size of the breasts and the uterine cervix in women taking the pill, but for the breast rather, at least in subgroups, increases the breast’s size and for the uterine cervix increases the size of the glandular compartment. Oral contraceptive use is correlated, as stated above, with no reduction in cancer risk, but rather with an increase in the risk for subgroups of users.

An increase in size of the breast and uterine cervix could be due to either fluid retention, augmented cell size or increased epithelial proliferation. In an investigation of women undergoing reduction mammoplasty operations, an increased epithelial cell proliferation of the breast has been seen before the first pregnancy after OC-use compared with never users especially during the first part of the menstrual cycle. The active proliferating cervical epithelium also increases in size after OC-use. Thus is seems probable that at least a part of the increase in organ size is due to active epithelial proliferation. A hypothesis has been presented previously by the author stating that permanent changes in hormones and hormone receptors after reproductive events early in life (such as a pregnancy or OC-use), occurring at the same time as organ growth and tumour initiation, may be of importance for the tumour biology detected decades later and offers a possible mechanism for cancer risks after reproductive events. The studies showing an increased risk of breast cancer and cancer of the
wards. Melasma, a facial pigmentation, is seen in increase during OC-use and usually persists after-
known that pigmentation on certain locations might be difficult to prove. It is, however, increase in size of the melanocyte compartment after u.v.-light exposure, but it has not been shown that this occurs especially after long term OC-use. The situation might be different for ovarian cancer as the number of ovolutions, rather than hormone exposure itself, may be the risk factor. It is believed that microtrauma to the ovarian stroma by each ovulation, increasing its proliferation, could be responsible for the association. Oral contraceptive use reduces the risk for ovarian cancer by up to 50%, possibly by inhibiting ovolutions. However, OC-use also reduces the size of the ovarian stroma. Because the mechanism for risk reduction in cancer risk to the ovary after OC-use may be related to an effect on ovolutions rather than directly hormonal, it is unclear if a reduction in size of the ovaries is relevant to the risk reduction.

In all organs, where OC-use has been found to affect the cancer risk in women, either by reducing or augmenting the risk, a relationship exists between OC-use and the organ size. A larger organ volume during/after OC-use is thus correlated with a higher risk.

Little is known about OC-use and its relationship to tumour development in other organs than the breast, ovary, uterus and the liver. Further information is lacking on possible effects from OC-use on the size of other organs. It has not been consistently shown that OC-use increases the risk of malignant melanoma, although some studies have suggested that this occurs especially after long term OC-use. The hypothesis would here propose that women need to experience a proliferation of melanocytes during/after OC-use in order to constitute a risk group. The number of melanocytes increases after u.v.-light exposure, but it has not been shown that there is a relationship between melanocyte density and frequency of melanoma formation. However, the hypothesis would focus on proliferating cells, and whether such a group exists, with an increase in size of the melanocyte compartment after OC-use, might be difficult to prove. It is, however, known that pigmentation on certain locations might increase during OC-use and usually persists afterwards. Melasma, a facial pigmentation, is seen in 23–25% of patients on oral contraceptives often in conjunction with increased pigmentation of nipples and genitalia.

Other important organs to investigate in the aspect of organ size and OC-use would be the salivary glands, lymph glands, the lungs, the gastrointestinal tract, and the thyroid.

The hypothesis presented in this paper would further propose that women who retain the original size of an organ (or actually its proliferative compartment) and have a normal physiologic size of the organ for a given age while on OCs, will experience the same risk as women not taking the pill.

The hypothesis also proposes that exogenous hormones given as OCs promote tumour development by increasing cell division and consequently increase the cell number of an organ at risk. This implies that steroid hormones do not need to act as initiating agents, but rather increase the likelihood for an initiator (a true mutagen) to transform a cell. “Promotion during initiation” would be an appropriate term for the OC–cancer relationship in humans.

**CONCLUSION**

The above suggests that it may be worth while to investigate OC-use and its possible effect on organ size and tumour risk of the same organ. In women now possibly experiencing a risk for breast cancer, liver cancer and cancer of the uterine cervix after OC-use, prospective studies should be launched to find out if women in whom breast, liver and cervical size increases during/after OC-use have the highest risk of cancer development in these organs. Further, different dosages of hormones and different compositions of OCs may possibly be studied in this aspect. as the studies cited with an increased risk so far reflect the use of high dose pills during the 1960s, and latency time has still been too short to assess any cancer risk by the more modern low dose pills. It may also be worth while to investigate other risk factors for tumours of reproductive organs in relation to possible effects on organ volumes prior to tumour development. However, as a proposal for continued research this hypothesis should not be used for prematurely changing prescription habits for modern OCs. The total positive and negative health effects from OC-use for all age groups is not yet known and a premature change of prescription habits could lead to an increase in the rate of abortions. Beside other unwanted social and medical effects abortion could by itself be a risk factor of breast cancer, although not all studies have consistently found abortions to be associated with breast cancer.
Acknowledgements — Supported by grants from the Swedish Cancer Society, Medical Faculty, Lund University and King Gustaf V’s Jubilee Fund.

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64 H. Olsson

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