

Presidential comment

IARC Monographs Program on Carcinogenicity of Combined Hormonal Contraceptives and Menopausal Therapy

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ABSTRACT

The World Health Organization International Agency for Research and Cancer (IARC), in June 2005, has classified combination hormone contraception and menopausal therapy as carcinogenic in humans. The IARC's distinction is to identify potential carcinogens associated with nutrition, environment and pharmaceutical products. They do not produce risk–benefit analyses for any country or population. Their conclusions are highly controversial in that no proof is presented for a causal relation of estrogens with reproductive cancer, be it plausibility according to mechanisms of action or experimental evidence in the animal model. Equating natural compounds like estradiol with defined carcinogens like asbestos, tobacco smoke as well as indispensable drugs such as aspirin and tamoxifen is of no substantial clinical relevance. Thus, there are no new reasons to change current management principles with combination hormone contraception and therapy.

INTRODUCTION

In June 2005, the IARC Monograph Working Group met at the World Health Organization International Agency for Research on Cancer (IARC) in Lyon, France, to assess the carcinogenicity of combined contraceptives and hormone therapy to humans. Their assessment will be reported as Volume 91 early next year. A press statement (no. 167) was released on July 29 (Reuters)¹. *Lancet Oncology* (August 2005) published a short concluding statement generated from this Meeting².

‘After examining all the evidence’, the Working Group classified combined oral contraceptives as well as combined estrogen–progestagen hormone therapy as carcinogenic in humans (group 1). In a variety of countries, the subsequent press and media response, with few exceptions, was more balanced than we have been accustomed to in recent years with this subject. Among other reasons, this may be related to the Working Group's distinction of identifying potential carcinogens associated with nutrition, environment and pharmaceutical products. Risk–benefit analyses are outside the scope of IARC Monograph Meetings. Thus, they do not quantitate estimates of the age-specific absolute risk at each cancer site, the availability and effectiveness of cancer screening, the availability, effectiveness and side-effects of cancer treatments, and other health and societal effects, both beneficial and adverse. However, as these factors vary throughout the world, the Group suggests that specific risk–benefit analyses be prepared for each country and population. Consequently, the Group

admits that its statement will not meet the overall net public-health outcome, be this of a beneficial or adverse nature other than cancer. The message is that any IARC classification by itself has no practical consequences. There is no reason to change current clinical practice, particularly when taking the risks of unwanted pregnancy into consideration. As before, prescription of oral contraceptives or menopausal hormone therapy is based on an individual risk–benefit assessment, provided account is taken of contraindications and regular visits to doctors or health-care professionals are made.

WHAT ARE THE ARGUMENTS OF THE IARC GROUP?

Oral contraceptives

There is a mention of ‘slightly increased risk of breast cancer in current and recent users of hormonal contraceptives’. This risk disappears 10 years after cessation of use and will be similar to that in never-users. The risk of cervical cancer is quoted as increasing with duration of use of combined oral contraceptives. Hepatocellular carcinoma would be seen more frequently in long-term users of combined oral contraceptives in populations with low prevalence of hepatitis B infection and chronic liver disease. On the other hand, decreases in the risk of endometrial and ovarian cancer have consistently been observed in women who used combined oral contraceptives. Longer duration of use would add to this reduction, and some reduction persists at least 15 years after cessation of use.

Combined menopausal therapy

There is strong mention that many epidemiological studies, including two large randomized trials, consistently demonstrated that a combination of estrogens and progestagens does increase the risk of breast cancer in women. Those studies confine this effect to current or recent users, the risk increasing with duration of use and exceeding that of women taking estrogen-only therapy. Endometrial cancer risks supposedly depend on the number of days that progestagens are included in the combination therapy. No sufficient evidence was acknowledged as concluding that hormonal therapy has a protective effect at any cancer site.

NO NEW INFORMATION ON RISKS

Already in 1987 and later also in 1999, the IARC analyzed existing epidemiological studies and could not document a relation with cancerogenesis^{3,4}. Breast cancer risk estimates were taken from the two re-analyses of 1996 (oral contraceptives) and 1997 (hormone therapy), taking 54 and 51 studies, respectively, into account, with a total of more than 50,000 cases of breast cancer and more than 100,000 controls^{5,6}. For the first time, absolute risks were established for oral contraceptive users below the age of 20, with only one additional case in 20,000 women. This risk increment was caused by doses of ethinylestradiol of 50 µg and above, was apparent within 1 year of use, was independent of the duration of use, and disappeared within 10 years of withdrawal. This was indicative of pre-existing breast cancer with oral contraceptives influencing its development. Tumors were almost entirely localized, with no spread, and life-long risk was not increased. Biology would support this contention, as oral contraceptives suppress ovarian sex hormone production, replacing it by synthetic hormones.

The new assessment of the IARC is founded on estimates of the breast cancer risk of combined contraception in 60 studies of 60,000 patients, i.e. based on almost the same data as before. But large studies published since 1999 did not show any increased risks; among these were a large American case-control study with 4575 cases and 4682 controls⁷, a German cohort analysis with 14 825 women, 12 519 of them on oral contraceptives⁸, as well as the large Women's Health Initiative (WHI) observational study with 161 899 women, 67 000 of whom were taking oral contraceptives⁹.

NO MECHANISTIC PROOF FOR A CAUSAL RELATION WITH CARCINOGENESIS

The IARC has based its classification of a 'carcinogen' on the evidence from experimental and clinical randomized studies showing that estrogens and progestagens (oral contraceptives and hormone replacement therapy) cause a rise in epithelial cell proliferation of the glandular breast². However, there are clinical and experimental data pointing to a minor proliferative action of synthetic versus natural sex steroids on both breast and endometrial epithelium¹⁰⁻¹³. This would suggest smaller risks as hormonal contraception suppresses ovarian estradiol secretion.

Whether these proliferating effects on normal epithelia, as a result of replication errors, may cause malignant transformation has not as yet been proven, although DNA repair is hampered by activated proliferation¹⁴. Standardized tests of mutagenicity with the end-point of 'gene mutation' have not provided proof for any mutagenic action. With the end-point of 'chromosomal mutation', numerous chromosomal aberrations (aneuploidy) have been observed with both natural and synthetic estrogens as well as progestagens. There is, however, no proof for sufficient strength of these effects to induce tumors¹⁵⁻¹⁷. All of this mechanistic investigation is essentially based on *in vitro* studies. Even today, we would not be able to discriminate hormonal tumor promotion from a causal relation with breast tumor induction¹⁸.

The classification of a compound as a carcinogen requires plausibility according to mechanisms of action and clear experimental proof for tumor induction in the animal model. Estrogens may accelerate the growth of occult breast tumors, with obvious likelihood, as 45-49-year-old women have occult breast lesions, with 39% chances of malignancy and 1.3% of cellular atypia¹⁹; on the other hand, a woman's life-time chance of clinically manifested breast cancer is 10% in Western populations. In reviewing the experimental literature, Liehr has classified estradiol as a weak carcinogen and a weak mutagen, inducing genetic lesions with low frequency²⁰.

Toxicity studies use animal models, which preferentially allow some prediction as to quantitative similarities of the investigated animal with human physiology. The mode of application, pharmacokinetics and pharmacodynamics, as well as target organs, should be comparable. However, species-specific effects of sex steroids on the endocrine system would not allow for the induction of hormone-sensitive tumors in rodents or dogs to be extrapolated to human conditions. Supraphysiologic doses of estradiol in mice may induce tumors of the glandular breast, pituitary, uterine endometrium and cervix, vagina and bone. Breast and pituitary tumors have been induced in rodents, and malignant kidney tumors in guinea pigs. There is no animal model where lower doses of estrogen were able to induce cancer. The fact, that simultaneous application of vitamin C would lower the incidence of estrogen-induced

kidney tumors, points to a causal role of catechol estrogens and quinones or free radicals, respectively²¹. However, all this knowledge is based on *in vitro* and/or animal studies. Consistent proof of any causal relation will only emanate from clinical studies with appropriate reference to epidemiology.

CLINICAL STUDIES DO NOT SUGGEST A CAUSAL RELATIONSHIP

The randomized, placebo-controlled WHI study provides a database for the clinical effects of hormone therapy, which, according to evidence-based medicine, has to be classified as level I. Estrogen monotherapy rather decreased breast cancer incidence, an effect which is close to statistical significance and which, with further follow-up, may indeed reach statistical significance²². With combined estrogen–progestagen therapy, one may extrapolate an association of menopausal hormone therapy with breast cancer. According to standards of evidence-based medicine, however, this association has to be restricted to WHI study conditions. A subsequent analysis by the WHI of the full estrogen plus progestagen study period revealed increased breast cancer risk in hormone-pretreated women only²³. This all happened because, in year five, there was an unexplained transient fall in the rates of diagnoses in the placebo group rather than a rise with combination hormone treatment. The small differences in absolute numbers of diagnoses between groups during the trial makes conclusions regarding the possible value of combination hormone therapy uncertain and devalues or invalidates the conclusions drawn from the initial WHI study^{24,25}.

Progestagens will normalize the long-term estrogen-associated incremental risk of endometrial cancer^{26–28} or even reduce it when given for a minimum of 12 days per treatment cycle^{29,30}. A substantial risk reduction of ovarian cancer is seen with oral contraceptives. For both endometrial and ovarian cancer, these effects are biologically plausible and have consistently been observed^{31–35}.

Cervical cancer is caused by human papillomavirus (HPV) infection^{36,37}. As its prevalence is not increased in women on oral contraceptives³⁸, there is no clinical evidence for causation. But the HPV-associated increased risk is up to 500-fold and the bias from more frequent sexual activity and Papanicolaou smears and other risk factors such as smoking would add to the risk; thus, it seems already impossible to differentiate any risk attributed to oral contraceptives. Relative risk estimates of oral contraceptives have been shown to vary up to the level of 2³⁸. The IARC presented only one reason for its classification of increased risk of cervical cancer with oral contraceptives, i.e. *in vitro* animal studies supposedly suggest an estrogen- and progestagen-dependent enhancement of the expression of certain human papillomavirus genes².

Also, the assumption of a heightened risk of hepatocellular carcinoma in long-term users of combined oral contraceptives in populations with low frequency of hepatitis B infection and chronic liver disease lacks any evidence from placebo-controlled investigation. The available evidence is based on a few case–control studies with insufficient case numbers, whereas studies from countries with frequent hepatitis-induced liver cancers revealed no effect of oral contraceptives. Again, the effects of causation and promotion cannot truly be distinguished. As these cancers are extremely rare, they have only little clinical relevance when contraindications are observed.

IARC LABEL 'CARCINOGENIC' OF NO SUBSTANTIAL CLINICAL RELEVANCE

The alleged incremental risks have all been introduced into package labeling and information leaflets with all marketed preparations for oral contraception and menopausal hormone therapy. Whether or not it is justified to classify combined oral contraceptives and combined estrogen–progestagen hormone therapy as carcinogenic to humans and thereby establishing a causal relationship is not communicated by the IARC press statement or short communication. Unless the Monograph discloses more relevant details, one should instead concentrate on the irritation and confusion caused in the lay public and media. Even when this decision is primarily based on *in vitro* and animal experimental investigation, applying supraphysiological doses of estrogens and progestagens for the induction of various tumors may only be correct in terms of pharmacotoxicology. However, its association with hormones and any pharmaceutical products in general is highly controversial. Given this, natural compounds like estradiol will be equated with asbestos or tobacco smoke as 'carcinogenic'. Moreover, indispensable drugs such as aspirin and tamoxifen, a diethylstilbestrol derivative, have been termed carcinogenic^{39,40}.

The rather small potential of the production of mutagenic or possibly 'carcinogenic' hormone metabolites needs to be compared to the daily exposure of mankind to strong carcinogens and mutagens. Humans are exposed daily to a variety of mutagens and carcinogens of an either environmental or nutritional origin; unspecific defense mechanisms of a broad spectrum (particularly cytochrome P450-dependent enzyme systems) will provide adequate detoxification^{15,41}. A cup of coffee, for example, contains a minimum of 19 defined carcinogens⁴², and heating food (boiling, baking, frying or barbecuing) will produce carcinogens which people ingest in large quantities^{17,41–43}. Evolution has provided mankind with adaptive responses; however, insufficient immune defense mechanisms (e.g. genetic traits) may allow for clinical expression of a carcinogen.

What are the consequences of the IARC's classification in terms of day-to-day clinical practice of oral contraception and menopausal hormone therapy? There are no new reasons to change current management principles with oral contraception and menopausal hormone therapy. Each patient must be counseled about the current data on the risks and perceived benefits of oral contraceptives and menopausal hormone therapy so that she can make appropriate, informed, individual decisions about starting, continuing or stopping treatment. Such discussion can be part of an annual risk–benefit analysis undertaken with each patient and in the context of timely screening protocols^{25,44}. Absolute rather than relative risk best serves the purpose of introducing a woman to her individual risks, particularly with respect to cancer. The risk of complication with oral contraceptives and menopausal hormone therapy remains an important clinical issue and is subject to discussions between individual patients and their care-givers.

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