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Short Communication

Hormonal Protection against Lung Cancer Instead of CT Screening

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Abstract

Low-dose CT screening for lung cancer is currently only recommended when the benefit-risk ratio is acceptable. This includes heavy smokers between the ages of 50 and 75. In this case, screening is expected to reduce mortality from this cancer by 20%. The alternative hormonal lung cancer prevention achieves better results. There is also an additional benefit in the form of improved lung function with hormone replacement therapy (HRT) in postmenopausal women. Already 17 years ago, a British study found that exogenously administered hormones in the form of combination pills reduced the risk of lung cancer in women of childbearing age by 50%. The same study showed that women after the menopause and with a history of HRT had a lung cancer risk reduced by a third (RR 0.62). With a history of pills plus HRT, the risk was halved (RR 0.52). This is also the result of a German study. With the combination pill, the risk of lung cancer was reduced by almost a third and similarly with HRT use for 7 years or longer (RR 0.69 and RR 0.59). A study of women with iatrogenic early menopause showed that this is a causal relationship. The risk of lung cancer was then significantly increased (RR 1.51). A study by an international lung cancer consortium found a lower reduced risk of lung cancer in those with a history of HRT (RR 0.77). This is because the duration of HRT use was not taken into account. In this study, the risk of small cell lung cancer was reduced by two thirds (RR 0.37). This was also true without taking the duration of HRT use into account. Hormonal cancer protection in postmenopausal women is achieved by maintaining beta-estrogen receptors. These have antiproliferative effects and promote apoptosis. In estrogen deficiency, these receptors regress and the alpha-estrogen receptors dominate, promoting proliferation. HRT counteracts the development of insulin resistance and thus reduces the risk of developing new cases of diabetes by a third or more. Disturbed glucose metabolism and hyperinsulinaemia are known to increase the risk of cancer. Since estrogens administered transdermally in low doses are sufficient to protect against cancer, they pose no danger to healthy women.

Product information/contents

CT lung cancer screening has more successful alternative

Key words: lung cancer early detection,lung cancer prevention,estrogens for cancer protection,cancer after,menopause

Introduction

Low-dose CT screening for lung cancer is expected to reduce mortality from this cancer by 20% in risk groups. For women, this cancer is a bigger problem with 5-year survival rates of 15% than breast cancer with 5-year survival rates of 87%, almost a factor of 6 difference. Too many false-positive CT findings are sometimes accompanied by risky clarification. This can hardly be expected to provide high levels of compliance. With hormonal lung cancer prevention, the risk of developing the disease is reduced by half or more. The threat of reduced lung function after menopause is also counteracted hormonally. There are hardly any risks to be expected with transdermal estrogen replacement. This cancer protection can be explained in a biologically plausible way. In Germany, 23.000 women develop lung cancer every year and 16,500 die from it. It is the second most common cause of cancer death in women. 70,000 women are diagnosed with breast cancer every year and 18,000 die from it every year. Around 87% are still alive after five years after the initial diagnosis; for lung cancer the figure is around 15% (1.2), i.e. almost a factor of 6 less. This means that the risk of lung cancer is as important as the risk of breast cancer. This appears to be the case with screening using low-dose CT. In the NELSON study (1.2) there were 2.5 deaths per 1,000 in a high-risk population in the CT screening group of 50 to 74 year olds and 3.3 deaths per 1,000 without screening. After 10 years, can this difference of 0.8 fewer deaths per 1,000 be considered a great success? It should be borne in mind that only 1 in 10 nodules discovered is cancer. The study authors call for very strict screening indications. Experts are currently examining which conditions can be expected to ensure successful screening. This radiological examination takes a few minutes and the use of contrast medium is not necessary. Screening is also promoted with a fifth to a quarter less radiation exposure than with conventional CT. Currently, 70%

of lung cancers discovered can no longer be treated curatively. Specialist societies only recommend CT screening if there is an acceptable risk-benefit ratio. These are heavy smokers between the ages of 50 and 75 or those who quit heavy smoking less than ten years ago. For these risk groups, the benefits are still so questionable that health insurance companies do not cover the costs. All of these uncertainties do not exist with hormonal lung cancer prevention. But dogmatic thinking (estrogens cause cancer) has so far led to ignoring successful studies showing an approximately 50% lower risk of lung cancer through hormone replacement in women aged 50 and over. This is the age at which CT screening should be used.

Not only one, but several studies confirm evidence

The 20% reduction in lung cancer mortality expected from CT screening is offset by significantly greater success with hormone replacement therapy with estrogens plus progestogens. This is achieved without radiation exposure and also has a variety of additional benefits. This also includes better lung function. HRT is cost-effective at under €200 per year. First of all, the question: "and the risk of breast cancer?" HRT reduces breast cancer mortality by half or more [3].More on that later. All of this may seem primarily utopian.

Royal College of General Practitioners study was "revolutionary"

This study on exogenously administered hormones and the risk of lung cancer in women was published 17 years ago [3]. In women of fertile age and using hormonal contraceptives, the risk of lung cancer was halved (RR 0.49). In women after menopause with a history of hormone replacement therapy (HRT), the risk of lung cancer was reduced by more than a third (RR 0.62). With a simultaneous history of hormonal contraceptives and HRT, the risk of lung cancer was reduced by half (RR 0.53).Two years earlier, a German study came to a similar conclusion [5].With hormonal contraceptives in the form of combination pills with EE plus progestin, the relative risk of lung cancer was reduced to RR 0.69 and with HRT use for 7 years or longer to RR 0.59.This was confirmed by a meta-analysis from 2013 [6] in 650,000 women suffering from lung cancer. This was particularly true for quite slim women with a body mass index below 25 (RR 0.65) who have few fat deposits for metabolizing testosterone from the ovaries and adrenal glands into estrogen via the aromatase enzyme. This applied to a lesser extent for non-smokers (RR 0.86). With iatrogenic early menopause, the risk of lung cancer increased significantly (RR 1.51; $p = 0.001$).These study results were hardly noticed in gynecology because they violated the ongoing dogma that "estrogens cause cancer". A review paper by the author on the subject was rejected by a professionally controlled journal on the grounds that "lungs are not of gynecological interest."

Social status as a risk of lung cancer

It is well known that the risk of cancer is increased in women with low social status and who often do not lead a health-conscious lifestyle. In gynecology, this applies to cervical cancer due to suboptimal genital hygiene in partner relationships. Associated with nicotine consumption, this means an even higher risk of infection in the genital area (including HPV). Analogously and biologically plausible, the risk of lung cancer is increased. This group of women is less likely to use the free screening services available in Germany to detect cervical cancer in its early stages, including its precursors. This group of women would hardly use lung cancer screening adequately. At the same time, HRT use depends on social status. Among gynecologists and partners of gynecologists, 8 out of 10 use HRT compared to 2 out of 10 of other women. This digression is appropriate because of the possible criticism: it is not hormone substitution, but higher social status that has a significant effect on the reduced risk of lung cancer. A Californian teacher study [7] with follow-up of 727 women with lung cancer (1993 to 2007). 4 out of 10 women died of this cancer after primary therapy. In those with estrogen replacement, lung cancer mortality was a third lower (RR 0.69). With over 15 years of HRT use, the success was even more pronounced (RR 0.60). Successes of long-term HRT use with up to two thirds less breast cancer mortality as in the Finland study [3] could not be achieved due to the use of unfavorable hormones in the USA.

International Lung Cancer Consortium 2013

A pooled analysis of women suffering from lung cancer [8th] found a lower risk of lung cancer in women with a history of HRT (RR 0.77). This benefit was particularly pronounced in small cell lung cancer (RR 0.37). The conclusion of the meta-analysis authors: Exogenous hormones protect against lung cancer. Two meta-analyses from 2020 confirmed the result. With a history of HRT, reduced mortality from lung cancer was found (RR 0.80 and RR 0.81) [9,10]. This corresponds to an expected 20% reduction in mortality through CT lung cancer screening - without any additional benefit and sometimes high diagnostic risks.

How does hormonal cancer protection come about?

Musial et al. [11] describe in their 2021 publication how estrogens determine the pathogenesis of lung cancer.If there are enough beta estrogen receptors (ÖR) in the lung cancer cells, this improves the prognosis of lung cancer sufferers. With a lack of estrogen, which is mandatory from the menopause onwards, the beta-ÖRs are reduced. This means that their antiproliferative properties and the promotion of apoptosis against cancer cells are missing. The risk of lung cancer then increases because the alpha-ORs with proliferation-promoting properties dominate. On this basis, the halving of overall mortality after breast cancer treatment among HRT users found in the nationwide Finland study is biologically plausible [3]. HRT causes an overexpression of beta-ÖR. This also explains: the longer the HRT use, the longer beta-ÖR are retained for cancer protection.

The majority of breast cancer is an estrogen deficiency cancer. The risk of breast cancer only increases significantly after menopause. If this is not observable into old age, it is due to earlier causes of death, especially CHD death. The latter is also related to estrogen, especially to the endogenous hormonal supply. Before menopause, healthy women with a non-risky lifestyle have little chance of dying from a heart attack. Early menopause at age 40 or earlier causes significantly increased CHD morbidity and mortality. HRT counteracts insulin resistance and reduces the risk of new diabetes by a third or more, according to the WHI study (12). Like diabetes, high insulin can be classified as a cancer risk, without going into the mechanisms here. The above information on the additional benefit of HRT makes it clear that the HRT co-indication "reduced risk of lung cancer" is worth consulting.

In fertile age, exogenous hormone protection is also worthwhile In heavy smokers, ovarian function is reduced. Just 20 packs of cigarettes per year double the risk of early menopause [13]. A meta-analysis of 14 studies [14] with European data found that hormonal contraceptives reduced the relative risk of lung cancer (RR 0.74) The reduced cancer risk is also higher than can be expected from lung cancer screening in risk groups. Plus an additional benefit. Combination pills (i.e. EE plus progestin combinations) used for 10 years or longer reduce the risk of ovarian cancer (with a poor prognosis such as lung cancer) by half or more. This protection lasts for 10 years or longer after you stop taking the pill. This would require a longer, separate presentation.

Why is HRT difficult to implement instead of lung cancer screening?

In gynecology, the guidelines for HRT are largely based on a level of knowledge that has long been outdated. The argument is based on large studies, most recently the publication of the WHI results from 2008. (12). In WHI, the study initiators, as internists, recorded a mostly unhealthy group

with an average age of 63 years. Then somatic HRT benefit is hardly to be expected. If vascular calcification is already evident, there is a risk of plaque mobilization as a failed “repair attempt”. However, HRT has somatic prevention goals: avoiding estrogen deficiency damage. If these are already present, then prevention is no longer possible and clinical events in the per mille range can occur. These were used for hormone bashing by doctors and the media. Only gynecologists and partners of gynecologists were not impressed by WHI uncertainty: 8 out of 10 continued to use HRT. This group of women is familiar with the German demand: all medical measures today should have additional benefits, not just the elimination of menopausal symptoms. Unlike in the USA, conjugated estrogens from mare urine have not been used for HRT in Germany for over 20 years. Because it is a mixture of hormones with some carcinogenic components that do not exist in the human body - and in different concentrations. In contrast, the estradiol used in Germany and the EU is clearly defined and the HRT preparations are dosed precisely. In US studies, MPA was mostly used as a progestin for emdometrium protection. Its metabolism takes place partly via biologically active estrogen metabolites. In risk groups, such as very obese women with large fat deposits, more of the body's own testosterone is converted into estrogen (via the splitting off of 1 carbon atom). This can lead to an excess supply of estrogen and thus to risks similar to other overdosed medications.

The balance of benefits clearly speaks in favor of estrogen instead of screening

High compliance with CT lung cancer screening is hardly to be expected. More information is needed for hormonal prevention. The latter rarely happens because it takes a lot of time and is often necessary repeatedly due to HRT advice from general practitioners/internists. The GKV consultation fee is just over €6. In addition, several health insurance companies in Germany advise their female members against HRT, in the irrational expectation of cost reductions. A European longitudinal study from 2017 [15].This showed that in women who were 24 to 48 years old at the start of the study and were observed for 11 years, lung function was reduced from menopause onwards to the same level as by smoking 20 cigarettes daily for 10 years before menopause. Lung function was assessed with spirometry and menopausal status with LH/FSH levels.

Gynecologists or general practitioners as cooperation partners?

For the majority of gynecologists, hormonal lung cancer prevention is a topic too far removed from the “core business”. Hormonal competence is not the rule, as it is not taught during medical studies or during further training (the author's experience in 35 years of university teaching for students and further trainees). The risks of HRT are hardly worth mentioning today. In case of doubt (are there obvious risks in the vessel walls?), transdermal estradiol substitution takes place. This avoids the liver first pass effect of oral HRT and does not activate the coagulation system. Therefore, VTE risks are hardly worth mentioning unless there is a family history of thrombosis and such problems have been ruled out during pregnancy and prior pill use (false pregnancy with very low hormone levels). Halving the risk of lung cancer through hormone replacement therapy can be successfully explained in a biologically plausible and biologically plausible way for women after menopause without hormone prejudice - according to the author's experience in university outpatient clinics. On the other hand, in addition to the CT radiation exposure, the many false-positive screening findings (9 out of 10 with a diameter of over 8 mm (16)) and the risks of clarification are difficult to convey. More interdisciplinary research activities are needed.

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