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# HRT to Protect Lung Function and Prevent Lung Cancer

*Mini Review*
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Author Details

*J Matthias Wenderlein**

Formerly Managing Senior Physician Ulm University Women's Hospital Prittwitzstraße, Germany

*Corresponding author

J Matthias Wenderlein, Formerly Managing Senior Physician Ulm University Women's Hospital Prittwitzstraße, Germany

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## Summary

Lung cancer screening is not very promising. According to a US population study, if lung nodules larger than 8 mm are discovered by chance, only one in 10 will be diagnosed with cancer. All prediction models overestimated the risk of cancer. This causes a lot of uncertainty for everyone involved. A successful alternative is hormonal lung cancer prevention, which can reduce morbidity and mortality by up to half - with long-term exogenous hormone intake from menopause onwards, with many additional benefits. It will take a lot of time before HRT guidelines make clear statements on this. This training article anticipates this, based on convincing studies. This can already be used for HRT advice.

In the lungs, as a paired organ with a large surface area, the blood-air barrier should be optimally maintained for as long as possible. This is more susceptible to disruption in women than in men and is therefore of gynecological interest. Women differ from men in the thorax volume in the ratio 4 liters to 5 liters and in the respiratory volume 90 l/minute to 110 l/minute. The difference in breathing limit volume is 110 l/minute to 160 l/minute. In women, the airways are smaller (nasal cavity, trachea, bronchi) and at rest, chest breathing dominates; in men, abdominal breathing dominates. In stressful situations, women's respiratory muscles have to do more mechanical work, with higher energy consumption (due to smaller airways, among other things) than men. During maximum physical exertion, women use 14% of their total O2 capacity, men only use 9%, for example when running the same distances. Women need a higher heart rate than men to absorb more O2. This digression (the author looked after competitive athletes in the outpatient clinic) explains why gynecology should deal with hormonal lung protection with endocrinological competence. COPD and its symptoms are hardly discussed here. This severe chronic obstructive pulmonary disease can shorten life up to 7 years and, in severe forms, is always fatal. Lung function can be objectively measured with spirometry, similarly to menopause status with LH/FSH values.

## HRT Protects Lung Function

The continuous decline in lung function has so far not been sufficiently correlated with decline in ovarian function and thus hormonal deficiency. In the years following menopause, this becomes clear and is of greater importance than chronological aging. This can be observed clinically in women with early menopause. A literature search is presented here, which cannot be presented in tabular form due to the different study concepts. The collectives and questions in the studies were too heterogeneous for this.

## Clinical Relevance is Confirmed By 20 Years of Follow-Up

A European longitudinal study that related lung function and ovarian function is exemplary. The results were published in 2017 [1]. At the start of the study, the women were 25-48 years old (n=1,438) and had no lung problems. 60% of the collective were of fertile age. 3,295 pulmonary function tests were carried out and the menopause status was objectively assessed using the LH/FSH laboratory. Spirometry FEV1 was reduced from menopause onwards, comparable

to 20 cigarettes/day for 2 years before menopause. (1 second capacity = maximum inhalation in 1 second after maximum exhalation). Lung vital capacity declined in the years after menopause, as with consumption of 20 cigarettes/day for 10 years before menopause.

Conclusion: With HRT, this development can be counteracted in good time from the menopause onwards in order to maintain respiratory health. The relationship was linear and there is no doubt about the causality.

## Can Loss of Lung Function after Menopause be Easily Explained?

Osteoporosis due to a lack of oil reduces the height of the BWK and this hinders the chest when inhaling and optimal diaphragm position is no longer achieved. Losing just 1 cm of body length within 11.4 years increases mortality by 15%. With a loss of 2 cm or more, the risk of death is increased by 74%. These data from Sweden/Denmark from 2021, published in the BMJ [2], mean for the study authors: body length from menopause onwards needs more attention as a key mortality indicator. The advantage is that women can become active themselves and may be more convinced by their own length measurements than by abstract bone density measurement values. In addition, with oil deficiency from the menopause onwards, there is more systemic and pulmonary inflammation (often without symptoms). This will probably motivate less to take HRT than self-determined loss of body length (measured at the same time of day at the same measuring point, with a 90° angle).

## Do We Need More Hormone Labs? No!

All HRT recommendations are accompanied by the advice: start HRT in good time. This is too vague and lab is indicated in exceptions. Climacteric symptoms provide the essential orientation. Analogous to this: hardly anyone would come up with the idea of making pain therapy dependent on laboratory values. Timely start of HRT in the interest of preventing osteoporosis and thus also lung function can obviously be based on the cycle history: irregular cycles and lasting over 40 days. This can be classified as a disturbed hypothalamic-pituitary-ovarian axis and is clinically associated with clinical relevant hormone deficit. Even mortality estimates are possible, the result of data that also appeared in the BMJ in 2021 [3]. 80,000 women up to the age of 46 who were observed up to the age of 24 were recorded. At the start of the study, the study participants were healthy. With irregular cycles lasting more than 40 days, the risk of dying before the age of 70 was increased in 4 out of 10. The comparison was made with women who had 4-week cycles. O2 transport and thus lung function are essential. Even premenopause can mean a risky hormone deficit and increase the risk of mortality - according to these long-term data. When it comes to hormonal lung protection, multidimensional thinking is required: Osteoporosis can begin individually earlier than bone density values indicate. Such measurements are cost-effective when the cycle history has such a high prognostic value. It is currently important to remember that we have the highest healthcare costs in the EU and are in the middle when it comes to life expectancy. The corona consequence - large numbers of illnesses will place a considerable financial burden on the healthcare system. The BGH would reject multi-class medicine.

## Do Not Expand Laboratory and Equipment Medicine

Back to the topic of lungs. There, inflammation causes a reduction in function. With an estrogen deficit, the risk of systemic and pulmonary inflammation increases significantly, not just cystitis risks including kidney risks. As a preventive measure, more hormone replacement should be used to counteract the risk of inflammation caused by hormone deficiency. In the case of recurrent urinary tract infections despite targeted antibiotic therapy, HRT is now used as a supplement and primarily. This means that in the case of early menopause: in addition to osteoporosis, you should also think about hormonal lung protection, especially if there are previous irregular and long cycles (almost the rule) and also consider the loss of body length in a consultation.

## Lung Function and Age at Menopause are Evidently Associated

There is an evaluation of 140,000 spirometry data from the GB Biobank [4]. Women who had menopause 45 years ago were compared with those who were 48-53 years old at menopause. Early menopause increased the risk of reduced lung function by 20%. This is relevant for gynecology. In women who had uterus removed with and without adnexal removal before menopause, the risk of reduced lung function was increased by 36%.

## Smoking Induces Earlier Menopause

In women who smoke cigarettes, it should be regularly pointed out that there is a risk of premature hormone deficiency, which means premature aging of all organ systems. The toxic effects of nicotine on ovarian cells can be quantified: 16-20 packs of cigarettes per year double the risk of early menopause [5]. The comparison was made with non-smokers. It should be remembered that transdermal estrogen replacement in medium to low doses does not increase the risk of VTE in otherwise healthy women. Bypassing the liver passage must be explained to those seeking HRT advice.

## COPD Incidence Increases Significantly After Menopause

Women without COPD before menopause have an increased risk of this chronic obstructive pulmonary disease, which is fatal in severe forms [6]. A biological explanation is increasing insulin resistance and diabetes from menopause onwards, which can be reduced by a third or more with HRT (including according to WHI data). This reduces the risk of infection, which primarily benefits lung function. Asthma is associated with increased lung inflammation, regardless of age and menopausal status.

## Slim Women with Higher Lung Risk

With a BMI below 23, the risk of pulmonary dysfunction is increased by a factor of 4. This applies up to BMI 28, but not for higher BMIs, with the exception of extreme obesity. Lung function does not decrease in overweight people up to 56 years of age [7]. Fat depots should be considered as an "estrogen source": via the aromatase enzyme, testosterone from the ovaries and adrenal glands is metabolized into biologically active estrogen. The comparison was between 45-56 year old women without HRT (n = 4,300). The menopause status was objectively assessed with LH/FSH [7]. Just 6 months of hormone deficiency almost doubled the risk of respiratory symptoms (RR 1.82). The comparison was with women aged 45 and over who had regular cycles. This relationship also held true for women without nicotine use.

Conclusion: if amenorrhea lasts more than 6 months, think not only about osteoporosis, but also about lung function.

## Before Starting HRT: Clarify Your Asthma and COPD History

According to Danish data [8], first-time hospitalizations for asthma account for 1.6% in women without HRT and 1.7% in women with HRT. For COPD the difference was 3.4% to 3.9-4.8%. These were

data up to 2010 after 13 years of observations (n=23,000), half with a history of HRT. The study authors explain this difference with "overlap syndrome": many additional indications contributed to hospitalization.

## Pulmonary HRT Benefit Achievable in the Short Term

In postmenopausal women without pulmonary diseases, spirometry was performed before and after three months of HRT: lung function improved spirometrically and in a clinically relevant manner [9]. Another study [10] found that cyclic HRT was most effective, followed by combined-continuous HRT. Progesterone was recommended as progestogen. Exclusive estrogen substitution did not result in any benefit for lung function.

## Outlook on Chronic Lung Problems

Nicotine consumption continues to increase among women. Lower amounts of nicotine than in men are dangerous. Therefore, female smokers have a 50% higher risk of mortality than men - plus a lower life expectancy. Estrogen replacement plus progesterone should be started in good time. The study data are so biologically convincing that further meta-analyses and lengthy prospective study results do not need to be awaited. Advice can begin. This also includes the following HRT benefits.

## HRT Reduces Lung Cancer Risk

The Royal College of General Practitioners is a professional body of general practitioners in the UK responsible for training, research and clinical standards. With 50,000 members, it is the largest royal medical college, founded in London in 1952. This institution has partnerships with foreign health organizations, runs international development programs and is responsible for postgraduate assessments. Studies from there should be taken seriously. There is also a study publication from 2006 [10] on the topic.

The lung cancer risk associated with pill and HRT use was of interest.

The main result: pill users have half the risk of lung cancer (RR 0.49). With HRT, the result must be viewed in a more differentiated manner. Lung cancer was diagnosed more frequently with current HRT use (RR 1.21) and significantly less frequently with a history of HRT (RR 0.62). This is not surprising because estrogens can have proliferative effects on the growth of existing lung cancers. This means that more cancers are discovered - without any prognostic disadvantages. This is because the time for metastasis processes can be shortened.

The conclusion of the study authors is therefore plausible: pill + HRT use in the anamnesis halves the risk of lung cancer (RR 0.53). At the time, the author's note said that these study results were of great importance for the healthcare system. General practitioners apparently think more globally than gynecologists, who more or less ignored the study results at the time.

## German Case-Control Study from 2003 Confirms the Above GB Study

In a German study, women were recorded after lung cancer therapy (1990-1996) (n= 811), with a control group (n= 912) [11]. Pill users had a lower risk of lung cancer (RR 0.69). This was independent of the duration of pill use and age, HRT for 7 years or longer almost halved the risk (RR 0.59). Smokers had a lower risk of lung cancer due to all exogenous hormones, as in the GB study cited above. In terms of lung cancer histology, the hormone groups did not differ from the control group. The remarkable thing about this study: the duration of hormone use was taken into account: longer use results in greater cancer protection.

## Lung Cancer More Common in Iatrogenic Early Menopause

A 2013 meta-analysis covered 650,000 women with lung cancer. The result: HRT protects against lung cancer, especially with BMI below 25 (RR 0.65) [12]. Non-smoking women also had HRT protection (RR 0.86). If menopause was brought forward iatrogenically, i.e. by uterine removal with or without adnectomy, then the risk of lung cancer increased significantly (RR 1.51) (p 0.001). In these women, the risk of cancer can hardly be offset with HRT because it was started too late and was used irregularly.

Conclusion for gynecology: Operations that advance menopause should be strictly indicated, also because of lung function.

## Social Status as a Risk of Lung Cancer

Many studies on the topic raise the objection that social status is not sufficiently taken into account. The lower the social status, the higher the risk of lung cancer. This methodological problem does not exist in the California teacher study from 2014 [13]. The test subjects had very similar social status, ideal for comparing with/without HRT and lung cancer risk. In the observation period 1995-2007, 727 lung cancers occurred and 441 died from it, i.e. 6 out of 10. Estrogen substitution reduced mortality from this cancer by a third (RR 0.69). This was already true for estrogen replacement for up to 5 years (RR 0.56) and HRT for more than 15 years (RR 0.60). This was not true for estrogen-MPA combinations, as the latter progestin is metabolized quite uncontrollably.

## Pill and Risk of Lung Cancer

The above study confirms that the appropriate gestagen must be used with HRT. Are the correct gestagens used in pills? There is also a meta-analysis from 2014 that included 14 studies [14]. When all data worldwide were summarized, there was no connection (RR 0.91). When the pills used in Europe were evaluated, protection against lung cancer was shown (RR 0.74). This explains some of the dubious results of meta-analyses: differences in studies are ignored, here related to different types and dosages of hormones worldwide.

## International Lung Cancer Consortium 2013

This cancer society, founded in the USA in 2008, also has cancer prevention as a research goal. For this purpose, a pooled analysis was carried out with women suffering from lung cancer (n=961) including a control group without cancer (n=2,609) [15]. When taking the pill, the risk of this second most common cancer was significantly lower in women who smoked (after breast cancer) (RR 0.81). Lower cancer risk was also found with HRT (RR 0.77). This was true for ERT and HRT, the latter being more efficient (RR 0.76 and RR 0.66). HRT was particularly successful in small cell lung cancer (RR 0.37). These women live about 12-18 months after therapy, with a miserable quality of life.

Conclusion of the study authors: exogenous hormones protect against lung cancer. It is surprising that gynecological research hardly addresses this topic. Hormonal primary prevention is underestimated due to a lack of hormonal competence. In our own medical studies, and even today, the topic of "hormones" is usually covered in 45 minutes in the main lecture per semester. If special seminars are offered, this is of no interest on the grounds that it is hardly relevant to the examination (too many examiners lack hormonal competence).

## Prospective Cohort Studies 2020

Does HRT protect against small cell lung cancer? This was verified using screening data (1993-2001) in 50-74 year olds with 13 years of observation (n = 75,587) [16]. In 11.5 years, lung cancer developed in 1.5% (n = 1,147). At that time (before WHI publication) half were

using HRT and a third had a history of HRT, with hormones that were not optimal at the time. Conjugated estrogens from mare urine are very heterogeneous in content and MPA is partly metabolized via estrogen-like substances. Nevertheless, the main result: lung cancer deaths can be reduced by HRT (RR 0.80). This also applied to pill use. There were no significant differences in reduced mortality between the two hormone user groups.

A further analysis published in 2020 had the above problem [17]. Ages 55-74 who did not primarily have lung cancer were included (n=77,911). With a history of HRT, cancer morbidity was reduced (RR 0.87) and also cancer mortality (RR 0.81). This also applied to current HRT use (without previous HRT history): morbidity and mortality were reduced (RR 0.84 and RR 0.80).The protection could have been clearer if there had been a detailed breakdown of the respective periods of use and current hormone composition. There is an exemplary study on breast cancer in Finland [18]: breast cancer mortality reduced by up to two thirds with long-term HRT use.

If the number of subjects was large, an evaluation after 15 and 20 years of HRT use versus no HRT experience would have been feasible. The author looked after women in university outpatient clinics who used HRT from the age of 50 to 70 and 80 - as a result of convincing risk-benefit information. Hormonal cancer prevention is highly rated.

## The Solution to the Puzzle: Beta ÖR

There is a publication from 2021 [19], the contents of which gynecologists and non-gynecologists should pass on to those seeking HRT advice. Estrogen determines the pathogenesis of lung cancer. In small cell lung cancer, the prognosis is even worse if only alpha-ÖR are present. If enough beta-ÖR are expressed, the prognosis is better. Over-expression can be achieved through endogenous and exogenously supplied hormones. The latter should be used in the event of a hormone deficiency from the menopause onwards to maintain beta-ÖR. These have antiproliferative and therefore cancer-protecting properties. These were discovered 10 years after the alpha-ÖR, with their cancer growth-promoting properties. These antagonistic effects were not sufficiently processed "mentally". The advantage "hormones cause cancer" also dominates. This shouldn't have a chance with gynecologists, because estrogen and progesterone also have antagonistic properties: proliferation and antiproliferation to ensure "ordered" cell growth. This is what evolution has designed, especially for pregnancy - for massive cell growth in embryonic and fetal times [20]. This evolutionary thinking can be passed on to those seeking advice on pills and HRT in a simple and understandable way.

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