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Hormonal dependent cancers in females. Epidemiological characteristics, trends and prevention possibilities

Diploma thesis

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Written Declaration

I declare that I completed the submitted work individually and only used the mentioned sources and literature. Concurrently, I give my permission for this diploma/bachelor thesis to be used for study purposes.

In Prague on   _____

Anne-Marthe Grislingås

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Introduction

I chose the theme of my diploma thesis for two reasons. One being my newly found interest in epidemiology and evidence based medicine, the other being my commitment to the treatment and prevention of diseases primarily affecting women.

My enthusiasm for evidence based medicine and epidemiology has steadily grown over the past years. As I'm approaching the end of medical school, friends and family apparently see it as their right to question the doctor-to-be about anything from local syphilis outbreaks to homeopathic lice repellent remedies. Initially not able to give satisfactory answers, I was forced to orient myself in a field I previously had not paid much attention to.

To my surprise, as I familiarized myself with the basics of epidemiological terminology and principles of proper trial conduction, I got increasingly interested in the topic. I could suddenly see examples of media's manipulation with statistics that I had not been able to spot before. I now understood how drug trials could be biased by improper randomization, something I normally wouldn't have given a second thought. It changed my view on many elements of medicine and its supporting sciences. It made me more aware of how easy it is to be flawed.

With this in mind, I delved into the vast amount of material to be found on my chosen topic, determined to do my job as thoroughly as possible, and to try to utilize as many quality sources as I could. My aspirations may have been a bit too high; but I've found general reviews and meta-analyses very useful for my work on this paper on hormone dependent cancers in females. It has been very interesting to work in this manner.

My main focus has been on breast cancer and its prevention. This is a topic most women can relate to, since (according to the American national cancer institute, based on current rates) 12.7 percent of western women born today will be diagnosed with breast cancer at some time in their lives. I am very much looking forward to following the development in both screening methods for and

treatment of hormone dependent cancers in the future, and hopefully play a role in the process myself.

1. Breast cancer

Breast cancer is the most common non-skin malignancy in women both in the developed and the developing world, comprising 16% of all female cancers, and accounting for more than 350,000 deaths per year worldwide.

Breast carcinomas can be divided into sporadic cases, related to hormonal exposure, and hereditary cases, associated with family history of germ-line mutations.
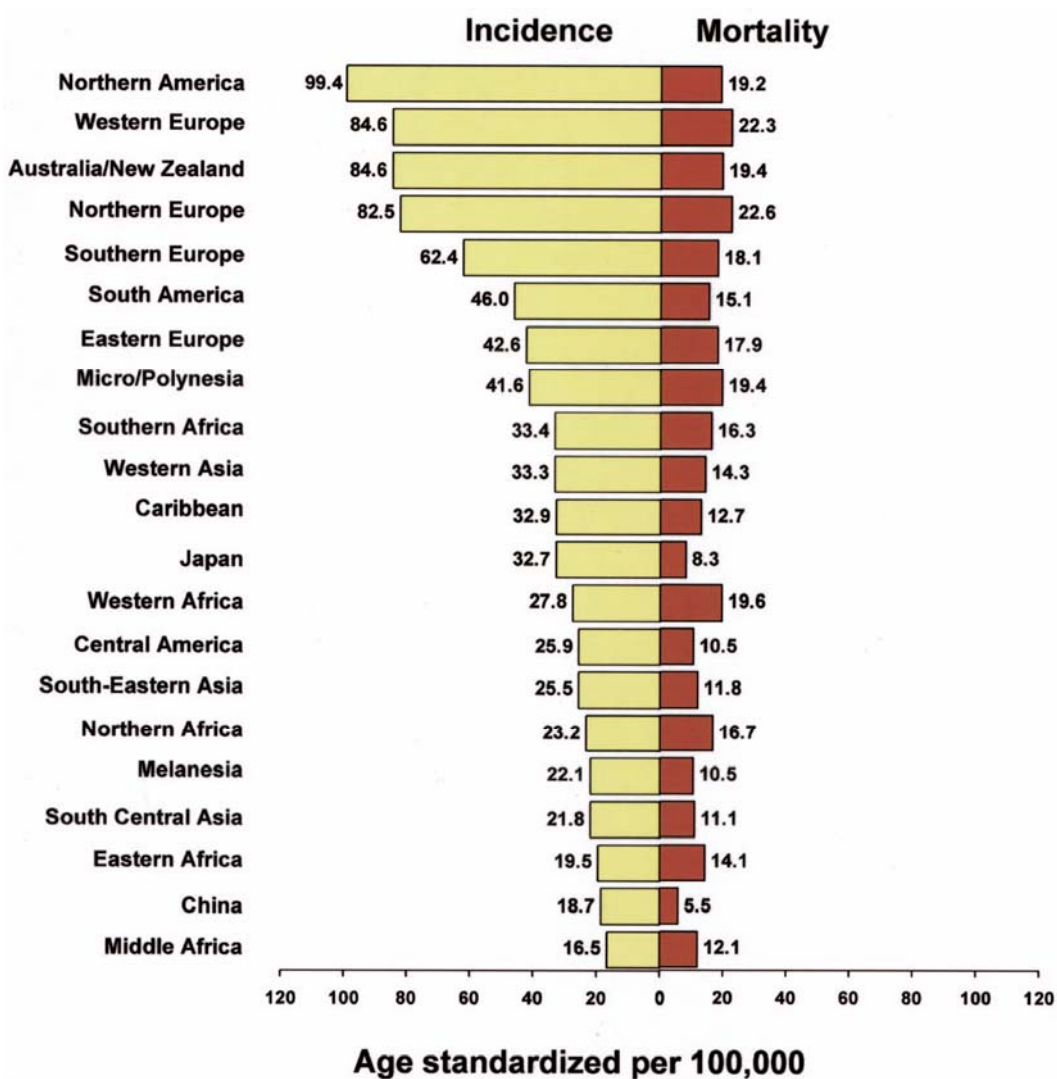
Several molecular pathways are known to have a role in breast cancer development and progression. Perhaps the most important pathway involves estrogen receptor alpha protein. The causal relationship between estrogen receptor expression and cellular responsiveness to estrogens and antiestrogens has been extensively studied in cell lines, animal models and humans and makes estrogen receptor one of the most important therapeutic targets in breast cancer. More than two-thirds of breast cancers show estrogen receptor expression at the time of diagnosis, and immunohistochemical detection of estrogen receptor expression is routinely used in making decisions on hormonal therapy (anti–estrogen receptor) for breast cancer. Current anti–estrogenreceptor treatment strategies include blocking by selective modulators (such as tamoxifen and raloxifene), destabilization and degradation of estrogen receptor by selective downregulators (such as fulvestrant) and disruption of estrogen synthesis (aromatase inhibitors, such as anastozole, letrozole or exemestane), any of which alone can result in a substantial decrease of tumor growth.

The degree of exposure to estrogen is a well-established risk factor for developing Estrogen Receptor-positive breast cancer. Estrogen is a steroid hormone that has a profound proliferative effect on normal human

mammary epithelium through its activation of ER-α, a classic nuclear hormone receptor. ER-α is overexpressed in as many as 70% of breast cancers; amplification of the ER-α gene appears to be a prominent mechanism, although it does not account for all cases of ER-α overexpression. Today, ER-α remains a very effective biologic target for breast cancer treatment and prevention, and antiestrogens are incorporated into the recommended treatment of all ER-α-expressing tumors.

1.1 Epidemiology and risk factors

Because of its high incidence and relatively good prognosis, breast cancer is the most prevalent cancer in the world today; there are an estimated 4.4 million women alive who have had breast cancer diagnosed within the last 5 years.


	Incidence	Mortality
Northern America	99.4	19.2
Western Europe	84.6	22.3
Australia/New Zealand	84.6	19.4
Northern Europe	82.5	22.6
Southern Europe	62.4	18.1
South America	46.0	15.1
Eastern Europe	42.6	17.9
Micro/Polynesia	41.6	19.4
Southern Africa	33.4	16.3
Western Asia	33.3	14.3
Caribbean	32.9	12.7
Japan	32.7	8.3
Western Africa	27.8	19.6
Central America	25.9	10.5
South-Eastern Asia	25.5	11.8
Northern Africa	23.2	16.7
Melanesia	22.1	10.5
South Central Asia	21.8	11.1
Eastern Africa	19.5	14.1
China	18.7	5.5
Middle Africa	16.5	12.1

Age standardized per 100,000

Age-standardized Incidence and Mortality Rates for Breast Cancer. Data shown per 100,000.

Breast cancer in the Czech Republic

The Czech National Cancer Registry has been maintained and updated in a standardized manner since 1976, and data on breast cancer is available for the Czech Republic covering the entire period from 1976 to 2005. Breast cancer is the most common cancer (excluding non-melanoma skin cancer) in Czech women, accounting for 17% of all newly diagnosed malignancies in the female population. The incidence trend in the entire monitored period has continuously increased – apart from the last few years when it has stabilised and even decreased. A total of 5,533 women were diagnosed with breast cancer in 2005, representing 105.4 breast cancer patients per 100,000 women. Breast cancer not only presents the major cancer incidence burden of the female population – it is also the most common cause of death from cancer in women. Approximately 1950 Czech women are dying of breast cancer each year, representing 37 deaths per 100,000 women. Despite the ever growing incidence of breast cancer, mortality has been stable in the long term.
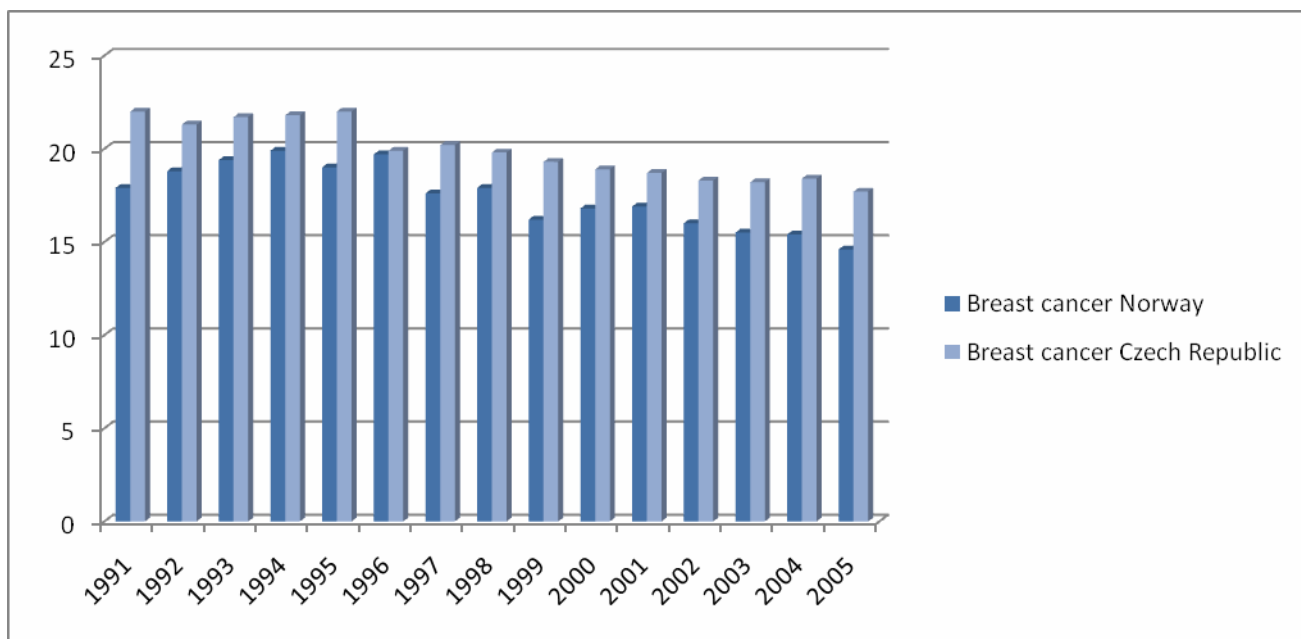
Breast cancer Age standardised incidence rate in Norway and the Czech Republic from 1991 to 2005. IARC numbers

Risk factors

The major risk factors for sporadic breast cancer are related to hormone exposure. The role of ovarian hormones in the development of breast cancer is demonstrated by studies of artificial menopause. Following ovarian ablation, breast cancer risk may be reduced as much as 75% depending on age, weight, and parity, with the greatest reduction for young, thin, nulliparous women

AGE AT MENARCHE: Women who reach menarche when younger than 11 years of age have a 20% increased risk compared to women who reach menarche when more than 14 years of age. Late menopause also increases risk, but the magnitude of the risk has not been quantified.

FIRST LIVE BIRTH: Women with a first full-term pregnancy at younger than 20 years have half the risk of nulliparous women or women over the age of 35 at their first birth. It is hypothesized that pregnancy results in

terminal differentiation of epithelial cells, thus removing them from the potential pool of cancer cells. The biologic basis of such differentiation is yet to be elucidated.

ESTROGEN EXPOSURE: Postmenopausal therapy slightly increases the risk of breast cancer in current users but might not increase the risk of death. Estrogen and progesterone together increase the risk more than does estrogen alone. ER-positive carcinomas are reported to be increased in this group. The effect of oral contraceptives is unclear, with some studies showing an increased risk of breast cancer in women taking oral contraceptives, while other studies have shown no change in risk. Women who are currently using combined oral contraceptives or have used them in the past 10 years are at a slightly increased risk of having breast cancer diagnosed. There is no evidence of an increase in the risk of having breast cancer diagnosed 10 or more years after cessation of use, and the cancers diagnosed then are less advanced clinically than the cancers diagnosed in never-users. Levels of endogenous sex hormones are strongly associated with breast cancer risk in postmenopausal women.

BREASTFEEDING: The longer women breast feed the more they are protected against breast cancer. The lack of or short lifetime duration of breastfeeding typical of women in developed countries makes a major contribution to the high incidence of breast cancer in these countries. The lower incidence of breast cancer in developing countries may be largely explained by the more frequent and longer nursing of infants. It has been hypothesized that inhibited ovulation during breastfeeding may suppress the risk of endometrial cancer.

OBESITY: Post-menopausal obese women are known to have higher endogenous estrogens than lean women due to the aromatization of androstenedione in adipose tissue. Obesity is also associated with reduced levels of sex hormone-binding globulin, which would further increase the amount of bioavailable estrogen. The effect of obesity on

breast cancer risk depends on a woman's menopausal status. Before menopause, obese women have a lower risk of developing breast cancer than do women of a healthy weight. However, after menopause, obese women have 1.5 times the risk of women of a healthy weight.

ALCOHOL CONSUMPTION: about 4% of the breast cancers in women in developed countries may be attributable to alcohol. The consumption of alcohol by most women in developed countries is relatively low, with about two-thirds consuming little or no alcohol each day. For women in developed countries who regularly drink alcohol, the lifetime risk of breast cancer is estimated to increase by about 0.7 per 100 women for each extra unit or drink of alcohol consumed on a daily basis. For example, the cumulative incidence of breast cancer by age 80 years is estimated to increase from 8.8 per 100 women who drink no alcohol to 10.1 or 100 who consume two alcoholic drinks daily and to 11.6 per 100 who consume four drinks daily.

DIET: Studies concerning breast cancer and dietary issues are controversial at best. Some studies show associations between consumption of fats and breast cancer. Some show connections between fat and animal protein consumption. These could influence endocrine metabolism, and thereby increase the risk of breast cancer.

AGE: Breast cancer is rarely found before the age of 25 years (except in certain familial cases) The incidence of breast cancer increases rapidly with age during the reproductive years and then increases at a slower rate after about age 50 years, the average age at menopause. The cumulative incidence of breast cancer among women in Europe and North America is about 2.7% by age 55, about 5.0% by age 65, and about 7.7% by age 75.2.

FIRST DEGREE RELATIVES WITH BREAST CANCER: The risk of breast cancer increases with the number of affected first degree relatives. However, the majority of cases occur in women without such a history.

1.2 Prevention and control

1.2.1 Prevention of breast cancer

Control of specific modifiable breast cancer risk factors, such as promoting healthy diet, physical activity and control of alcohol intake, overweight and obesity, could eventually have an impact in reducing the incidence of breast cancer in the long term.

1.2.2 Screening modalities for breast cancer

Mammography

Mammography screening is the only screening method that has proven to be effective. It can reduce breast cancer mortality by 20 to 30% in women over 50 yrs old in high-income countries when the screening coverage is over 70%. (IARC 2008)

Mammography utilizes ionizing radiation to image breast tissue. The examination is performed by compressing the breast firmly between a plastic plate and an x-ray cassette that contains special x-ray film. For routine screening in the United States, examination films are taken in mediolateral oblique and craniocaudal projections. Both views should include breast tissue from the nipple to the pectoral muscle. Mammography can identify breast cancers too small to palpate on physical examination and can also find ductal carcinoma in situ (DCIS), a

noninvasive condition. Cancer-related survival is better in screened women than in nonscreened women.

Sensitivity depends on several factors, including lesion size, lesion conspicuity, breast tissue density, patient age, the hormone status of the tumor, overall image quality, and interpretive skill of the radiologist. Overall sensitivity is approximately 79% but is lower in younger women and in those with dense breast tissue. Overall specificity is approximately 90% and is lower in younger women and in those with dense breasts. International comparisons of screening mammography have found that specificity is greater in countries with more highly centralized screening systems and national quality assurance programs (e.g. USA). Such comparisons may be confounded, however, by other social, cultural, or economic factors that can influence the performance of mammography screening. No improvement in cancer detection was noted in these studies despite the higher recall rate.

Harms of screening

Mammography screening may be effective in reducing breast cancer mortality in certain populations. As with any medical intervention, it has limitations, which can pose potential harm to women who participate. These limitations are best described as false-negatives (related to the sensitivity of the test), false-positives (related to the specificity), overdiagnosis (true positives that will not become clinically significant), and radiation risk.

ADDITIONAL INTERVENTIONS: Women with abnormal screening test results have additional procedures performed to determine whether the mammographic finding is cancer. These procedures include additional mammographic imaging (e.g., magnification of the area of concern), ultrasound, and tissue sampling (by fine-needle aspiration, core biopsy, or excisional biopsy).

FALSE SENSE OF SECURITY: Assuming an average sensitivity of 80%, mammograms will miss approximately 20% of the breast cancers that are present at the time of screening (false-negatives). If a woman does not seek medical attention for a breast symptom or if her physician is reluctant to evaluate that symptom because she has a "normal" mammogram, she may suffer adverse consequences.

A false-positive result, on the other hand, may lead to significant psychological stress, with women experiencing worry that affects their mood or functioning, even though subsequent testing rules out a cancer diagnosis.

RADIATION EXPOSURE: Radiation exposure is a known risk factor for the development of breast cancer. For women older than 40 years, the benefits of annual mammograms may outweigh any potential risk of radiation exposure due to mammography.

OVERDIAGNOSIS: Overdiagnosed disease is a neoplasm that would never become clinically apparent prior to a patient's death without screening. An example is a tumor that is found by mammographic screening that would never be evident otherwise. Because cancers that will progress cannot be distinguished with certainty from those that will not, these tumors are often treated (with surgery and possibly with radiation, chemotherapy, and hormonal therapy). This treatment would constitute overtreatment because it would not confer a benefit to the woman.

Mammography in Norway

In Norway, all women between the ages 50 and 69 are invited to a mammography screening every two years. This screening started in 1996.
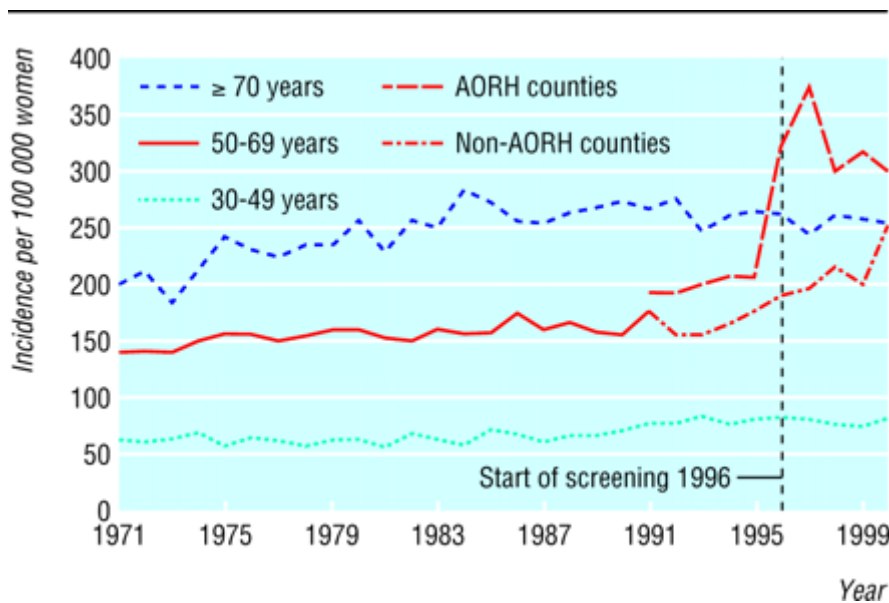

The introduction of mammographic screening programmes was associated with more than a 50% increase in the incidence of invasive breast cancer for the age group 50-69 years. It was expected that most of this increase would be compensated for by falling incidence rates when the women are no longer invited for screening, but there has been no significant reduction in incidence for the age group 70-74 years. A prospective cohort study of cancer incidence in Norway and Sweden concludes that after the introduction of screening programmes in Norway one third of all cases of invasive breast cancer in the age group 50-69 are overdiagnosed. The level of overdiagnosis in nationwide mammography screening is much higher than previously thought, and the Norwegian Medical Association has focused on informing women about this aspect of screening to allow them to make informed choices about further procedures.

Breast self-examination

Monthly breast self-examination (BSE) is frequently advocated, but evidence for its effectiveness is weak. Data from two large trials do not suggest a beneficial effect of screening by breast self-examination but do suggest increased harm in terms of increased numbers of benign lesions identified and an increased number of biopsies performed. At present, screening by breast self-examination or physical examination is not recommended. However, the practice of BSE has been seen to empower women, taking responsibility for their own health. Therefore, BSE is recommended for raising awareness among women at risk rather than as a screening method.

The method involves the woman herself looking at and feeling each breast for possible lumps, distortions or swelling. She looks in the mirror for visual signs of dimpling, swelling, or redness on or near the breasts. The woman then palpates her breasts with the pads of her fingers to feel for lumps (either superficial or deeper in tissue) or soreness. Finally, women who are not breastfeeding gently squeeze each nipple to check for any discharge.
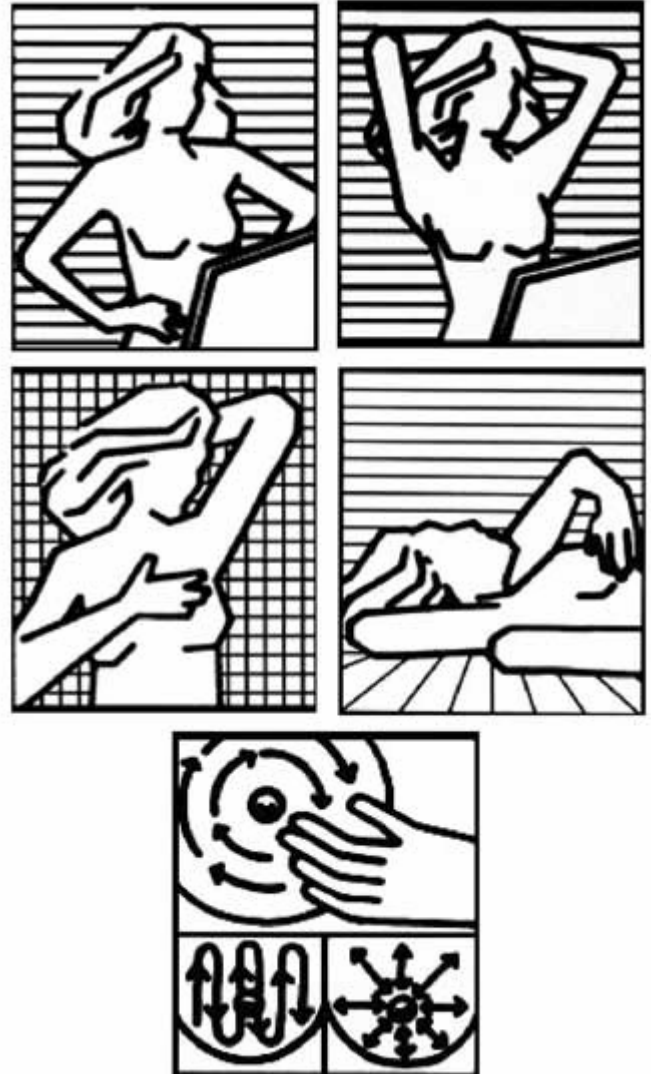
2. Endometrial cancer

Endometrial cancer is the most common invasive cancer of the female genital tract. Rates vary worldwide and are highest in white women in Western populations. Despite their high frequency, endometrial cancers arise mainly in postmenopausal women, causing abnormal bleeding, permitting early detection and cure at an early stage.

2.1 Epidemiology and risk factors

In Western populations endometrial cancer is most commonly found between the ages of 50 and 65 years, and is rare before the age of 40 (Figure 2). The peak incidence occurs in the post-menopausal age group.

Mortality rates for endometrial cancer have declined by about 60% since the 1950s. Since the mid-1980s the incidence has remained steady.

Menstrual factors: Most studies have found that early age at menarche, generally defined as before age 11 or 12 years, is associated with a 1.5 - 4-fold increase in risk of endometrial cancer. An association between endometrial cancer and late age at menopause has also been consistently reported.

Reproductive factors: Nulliparity and infertility are factors associated with increased risk of developing endometrial cancer, whereas multiparity is a protective factor, with decreasing risk with increasing number of children. Late ages at a first birth also appears to reduce risk. Induced abortions are associated with slight risk increases.

Estrogens: The majority of conditions known to influence risk of endometrial cancer can be directly or indirectly related to reproductive

hormones, in particular estrogens. Women with elevated endogenous estrogen levels have an increased risk of endometrial cancer. Conditions such as Polycystic Ovarian Disease (Stein-Leventhal Syndrome) and estrogen-secreting ovarian tumors appear to be especially linked to the occurrence of endometrial cancer in young women. The diagnosis of polycystic ovarian syndrome has been made in up to 30% of cases with endometrial cancer in selected groups of pre-menopausal women.

Hormone replacement therapy: Endometrial cancer risk increases substantially with long duration of unopposed estrogen use, and this increased risk persists for several years after discontinuation of estrogen.

Oral contraceptives: Use of the combined oral contraceptive pill (estrogen plus progestogen) reduces the risk of endometrial cancer. Long-term use of combined oral contraceptives appears to reduce the risk further, and the protective effect lasts for 20 or more years after discontinuation. (In contrast, sequential oral contraceptives marketed in the 1960s and 1970s (usually in the form of a relatively high-dose long-duration estrogen followed by a low-dose, short-duration progestogen), led to a dramatically increased risk of endometrial cancer in the late 1970s and early 1980s, and its subsequent discontinuation.)

Tamoxifen: Drugs that have an anti-estrogenic effect, in particular tamoxifen, are often used as adjuvant therapy for women with breast cancer. Case reports as well as the results from clinical trials in women with breast cancer have highlighted an increase in endometrial cancer resulting from use of these anti-estrogens.

Obesity: As previously stated, post-menopausal obese women are known to have higher endogenous estrogens than lean women due to the aromatization of androstenedione in adipose tissue. Diabetes and hypertension have also been linked to increased risk of endometrial cancer, but it is unclear if these are independent risk factors or merely markers of obesity.

Smoking: Current epidemiologic evidence indicates that cigarette smoking reduces the risk of endometrial cancer. The mechanism for this is unclear, with hypotheses including less obesity among smoking women, earlier menopause in smoking women, and the effect of smoking on endogenous estrogen metabolism.

Diet, alcohol and exercise: Findings suggest that women who avoid being overweight and who consume a diet low in plant and animal fats and high in complex carbohydrates are at a reduced risk of endometrial cancer. There is no association between alcohol consumption and endometrial cancer. The close relationships between diet, physical activity and body mass have made it difficult to assess the independent risks of the three on endometrial cancer. Whether physical activity plays a role via its association with obesity or whether it has an independent effect on risk of endometrial cancer is not clear. It is however clear that increased levels of physical activity reduce serum estrogen levels.

2.2 Prevention and control

Modifiable risk factors

Use of combination oral contraceptives, and combination estrogen-progestin for replacement therapy.

Control of obesity, which accounts for a substantial proportion of endometrial cases worldwide. A study conducted among European countries estimated that between 26% and 47% of endometrial cancer cases can be attributed to overweight and obesity. The same group conducted a meta-analysis of studies which examined the relationship between obesity and endometrial cancer.

Women should also be encouraged to breastfeed, and to maintain a certain level of physical activity.

<u>Screening</u>

Measuring endometrial thickness with transvaginal ultrasound and endometrial sampling with cytological examination have been proposed as possible screening modalities for endometrial cancer. The Papanicolaou test, used successfully for screening for cervical cancer, is too insensitive to be used as a screening technique for the detection of endometrial cancer.

Benefits: There is no evidence that screening by ultrasonography (e.g., endovaginal ultrasound or transvaginal ultrasound) or Endometrial Sampling (Biopsy) reduces mortality from endometrial cancer. Most cases of endometrial cancer are diagnosed at low stage because of symptoms, and survival rates are high.

Harms: Screening asymptomatic women can result in unnecessary additional biopsies because of false-positive test results. Risks associated with false-positive tests include anxiety and complications from biopsies (discomfort, bleeding, infection, and rarely, uterine perforation).

3. Ovarian cancer

Ovarian cancer is the most common cause of cancer death from gynecologic tumors in the industrialized world. Early disease causes minimal, nonspecific, or no symptoms. Therefore, most patients are diagnosed in an advanced stage. Overall, prognosis for these patients remains poor. Standard treatment involves aggressive debulking surgery followed by chemotherapy. Many histological types of ovarian tumors are described. However, more than 90% of malignant tumors are epithelial tumors.

The pathogenesis of ovarian carcinoma remains unclear. Several theories have been proposed to explain the epidemiology of ovarian cancer including the theory of "incessant ovulation" (repeated cycles of ovulation-induced trauma and repair of the ovarian surface epithelium at the site of ovulation), gonadotropin stimulation, excess androgenic stimulation, and inflammation. Associated risk factors for ovarian cancer support some or all of these hypotheses.

3.1 Epidemiology and risk factors

Ovarian cancer is the second most common cancer of the female reproductive system and the leading cause of death from gynecologic malignancies.

The risk for developing ovarian cancer increases with age. Ovarian cancer, rare before age 40, increases steeply thereafter and peaks at ages 65-75. Most cases occur after menopause, which usually takes place around the age of 51. Over 50% of all ovarian cancers occur in women older than age 65.

Over the last three decades, ovarian cancer incidence has remained stable in high-risk countries, while an increasing trend has been reported in low-risk countries. Despite recent advancements in treatment, the overall five-year survival rate continues to be low (39%). Over 70% of ovarian tumors are diagnosed when regional or distant involvement has already occurred, causing survival rates to remain stable.

Oral contraceptive use is consistently associated with a decreased risk of ovarian cancer and may operate through preventing the trauma from repeated ovulation by lowering exposure to gonadotropins. No one theory, however, explains all the associated risk factors.

Postmenopausal use of HRT (hormone replacement therapy) is associated with an increased risk of developing ovarian cancer.

Obesity is associated with an increased mortality from ovarian cancer. In cohort studies, height and body mass index (BMI), including high BMI during adolescence, were associated with an increased risk of ovarian cancer, suggesting a role for diet and nutrition during the adolescent period.

Family history plays an important role in the risk of developing ovarian cancer. The lifetime risk for developing ovarian cancer is 1.6% in the general population. This compares to a 4-5% risk when 1 first-degree family member is affected, rising to 7% when 2 relatives are affected. A history of breast cancer increases a woman's risk of developing ovarian cancer,

Fewer than 5% of all ovarian cancers have a hereditary predisposition. Clearly defined syndromes include Breast/ovarian cancer syndrome (BRCA 1 mutation associated) and Lynch II syndrome (hereditary nonpolyposis colorectal cancer).

Factors associated with a *decreased* risk of ovarian cancer include:

(1) using oral contraceptives (The protective association increases with the duration of oral contraceptive use and persists up to 25 years after discontinuing oral contraceptives.)

(2) having and breastfeeding children (Women who have been pregnant have a 50% decreased risk for developing ovarian cancer compared to nulliparous women. Multiple pregnancies offer an increasingly protective effect.)

(3) having a bilateral tubal ligation or hysterectomy, and

(4) having a prophylactic oophorectomy.

3.2 Prevention and control

The diagnosis of ovarian cancer could benefit from screening. Screening methods for ovarian cancer include pelvic examination, abdominal and transvaginal sonography, color flow Doppler, and serum CA-125 levels. Sonography and CA-125 are the most promising and most extensively studied.

Transvaginal sonography

With this method, a ultrasonic sound generator is inserted into the vagina to obtain a clearer image than can be obtained from the body's surface. The ultrasound image is then used to calculate the volume of the ovaries. An abnormally large volume or an unusual echo is indication for further tests. Transvaginal sonography screening causes a decrease in stage at detection. Further study is needed to determine if annual TVS screening will significantly reduce ovarian cancer mortality. The cost for TVS screening is reasonable and is well within the range of that reported for other screening tests.

Serum tumor markers

Among the serum markers, CA-125 has been studied most extensively. Isolated values of CA-125 lack adequate sensitivity or specificity, but when monitored over time, serial CA-125 values can achieve a specificity of 99.6%. However, sensitivity is limited and CA-125 may only be expressed by 80% of early-stage cancers.

Since its discovery, serum CA-125 level has been widely used as a marker for a possible epithelial ovarian cancer in the primary assessment of a pelvic mass. In this setting, false-positive results may derive from several conditions, especially those associated with peritoneal inflammation, such as endometriosis, adenomyosis, pelvic inflammatory disease, menstruation, uterine fibroids, or benign cysts. Malignancies other than ovarian cancer can also increase CA-125 levels, but the most marked elevations (>1500 U/mL) are generally seen with ovarian cancer.

The primary use of CA-125 measurement is to monitor the disease status of patients with ovarian cancer, such as detecting early recurrence or assessing chemoresponse during chemotherapy.

High specificity is important in screening strategies for ovarian cancer because a positive test result generally requires definitive surgical assessment, and combination test strategies have been tried to improve the predictive value of CA-125.

Conclusion

The cancerogenesis of breast, endometrial and ovarian carcinomas is a hormonally dependent process.

Evidence implicating estrogen as a key breast carcinogen comes from various lines of investigation. Traditional epidemiologic studies demonstrate associations between estrogen exposure, both exogenous and endogenous, and increased breast cancer risk.

Screening mammography in women aged 40 to 70 years decreases breast cancer mortality. The benefit is higher for older women, in part because their breast cancer risk is higher. The low survival rates in less developed countries can be explained mainly by the lack of early detection programmes, resulting in a high proportion of women presenting with late-stage disease.

In my opinion, the key is to ensure that the women are fully informed of both benefits and harms of mammographic screening, reducing the psychological stress of false positive results.

Summary

Breast cancer is the commonest cause of cancer death in women worldwide. Rates vary about five-fold around the world, but they are increasing in regions that until recently had low rates of the disease. Many of the established risk factors are linked to estrogens. Risk is increased by early menarche, late menopause, and obesity in postmenopausal women, and prospective studies have shown that high concentrations of endogenous estradiol are associated with an increase in risk. Childbearing reduces risk, with greater protection for early first birth and a larger number of births; breastfeeding probably has a protective effect. Both oral contraceptives and hormonal therapy for menopause cause a small increase in breast-cancer risk, which appears to diminish once use stops. Alcohol increases risk, whereas physical activity is probably protective. Mutations in certain genes greatly increase breast-cancer risk, but these account for a minority of cases.

Endometrial cancer is the fourth most common cancer in women and ranks eighth in terms of cancer mortality. Incidence rates have remained steady since the mid-1980s, with peak occurrence in the post-menopausal age group. There are wide differences in incidence across countries, with much higher rates seen in women in Western populations than in other populations. Most risk factors for carcinoma of the endometrium appear to be reproductive or hormonally-related; little is known about genetic influence on risk of endometrial cancer. Many risk factors appear to relate, directly or indirectly, to estrogenic

stimulation of the target endometrial epithelium. Factors such as early age at menarche, late age at menopause, nulliparity and infertility are all associated with an increased risk of endometrial cancer, as is abortion. Clinical conditions such as the Stein-Leventhal syndrome and use of unopposed estrogen replacement therapy, which raise estrogen levels, increase risk, while use of the combined oral contraceptive pill decreases risk (effects of both treatments persist for years after cessation). Evidence of a positive association between tamoxifen and endometrial cancer remains inconclusive. Increased risks have been seen consistently with obesity, diabetes, hypertension, and decreased risks with smoking, low-fat diets and physical exercise, although given the interrelationship of many of these, their independent effects are not clear. Again, the influences of these conditions on risk of endometrial cancer may all be mediated to some degree by estrogen.

Ovarian cancer represents the sixth most commonly diagnosed cancer among women in the world, and causes more deaths per year than any other cancer of the female reproductive system. Despite the high incidence and mortality rates, the etiology of this disease is poorly understood. Established risk factors for ovarian cancer include age and having a family history of the disease, while protective factors include increasing parity, oral contraceptive use, and oophorectomy. Lactation, incomplete pregnancies, and surgeries such as hysterectomy and tubal ligation may confer a weak protective effect against ovarian cancer. Infertility may contribute to ovarian cancer risk among nulliparous women. Other possible risk factors for ovarian cancer include postmenopausal hormone-replacement therapy and lifestyle factors such as cigarette

smoking and alcohol consumption. Many of the causes of ovarian cancer are yet to be identified.

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