Charles University 3rd Faculty of Medicine

PRIMARY AND SECONDARY PREVENTION OF BREAST CANCER

By

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April 2006

CONTENTS

1. INTRODUCTION

Breast cancer is the most common cancer and the second most common cause of death from cancer in women. Because of the high frequency of the disease and the esthetic and symbolic value invested in the breast, breast cancer has always been a source of severe distress to patients and their families. For the same reasons, breast cancer research has increased dramatically during the last 2 decades, resulting in extraordinary progress in our understanding of the disease and in new, more efficient and less toxic treatments. Furthermore, the diffusion of knowledge, the medical advancements, and the increased public awareness have led to earlier diagnosis at stages usually amenable to complete resection and potential cure of the disease. In this paper concentration will be on prevention of breast cancer including primary prevention which is the elimination of risk factors for the disease in asymptomatic persons which aim to reduce the incidence of new cases in a population, second prevention is earl detection and treatment of disease but its important to keep in mind that secondary prevention detect cancer but does not decrease their occurrence. It can however reduce mortality.

Frequency: The American Cancer Society estimated that 193,700 new cases of breast cancer (31% of all cancers) would be diagnosed in 2001 in the United States, making breast cancer the most-diagnosed cancer in women. The true incidence rates of breast cancer have been stable from 1987-1996 after a constant increase since 1979 (increase of 1% per y from 1979-1982; 4% per y from 1982-1987). The lack of decline of breast cancer incidence in the 1990s contrasts with a slight decline (decline of 1.3% per y from 1992-1997) of the incidence rate of cancer for all sites.

Although the death rate from breast cancer has decreased an average of 2.2% per year from 1990-1997, the recorded number of deaths from breast cancer has remained stable, at approximately 43,000 per year. Deaths dropped to 41,737 in 1998 after reaching the highest number, 43,844, in 1995. Among women aged 20-59 years, breast cancer is the leading cause of death from cancer. However, lung cancer remains the leading cause of death from cancer in women aged 60 years or older.

2. CLINICAL

In the past, the great majority of patients presented with a painless palpable mass. Although more than 80% of palpable masses are benign, the decision to observe such lesions should be made only after careful clinical, mammographic, and pathologic workup. Cystic lesions identified clinically or on ultrasound images should be explored using fine-needle aspiration (FNA) biopsy. Nonbloody fluid and complete resolution of the cyst confirm its benign nature. If the fluid is bloody or the cyst does not resolve after aspiration or has a complex appearance on the ultrasound image, a biopsy is indicated.

Other symptoms, such as breast pain or deformity, nipple discharge, and erythema or skin ulceration, occasionally occur. Patients with Paget disease present with a long-standing eczematoid rash of the nipple-areola complex, itching, tenderness, burning, and occasional bloody discharge from the nipple. Skin dimpling, the result of shortening or retraction of the Cooper ligaments induced by the tumor, does not have prognostic value, while the ominous peau d'orange sign reflects the invasion of the subdermal lymphatic plexus and portends a shortened survival.

Symptoms related to distant metastases, such as bone pain, dyspnea, or meningitic syndrome, are encountered in some cases.

In current practice, increasing numbers of breast cancers are mammographically diagnosed in the preclinical stage. Screening mammography has resulted in earlier diagnosis of breast cancer, which has translated in recent years into a 25% improvement in the mortality rate related to breast cancer. Mammographic signs suggestive of cancer include architectural distortions, microcalcifications, or masses. These changes require further evaluation using diagnostic mammograms with or without ultrasound. Biopsies are indicated if these changes are confirmed. Features helpful in the evaluation of palpable breast masses are as follows:

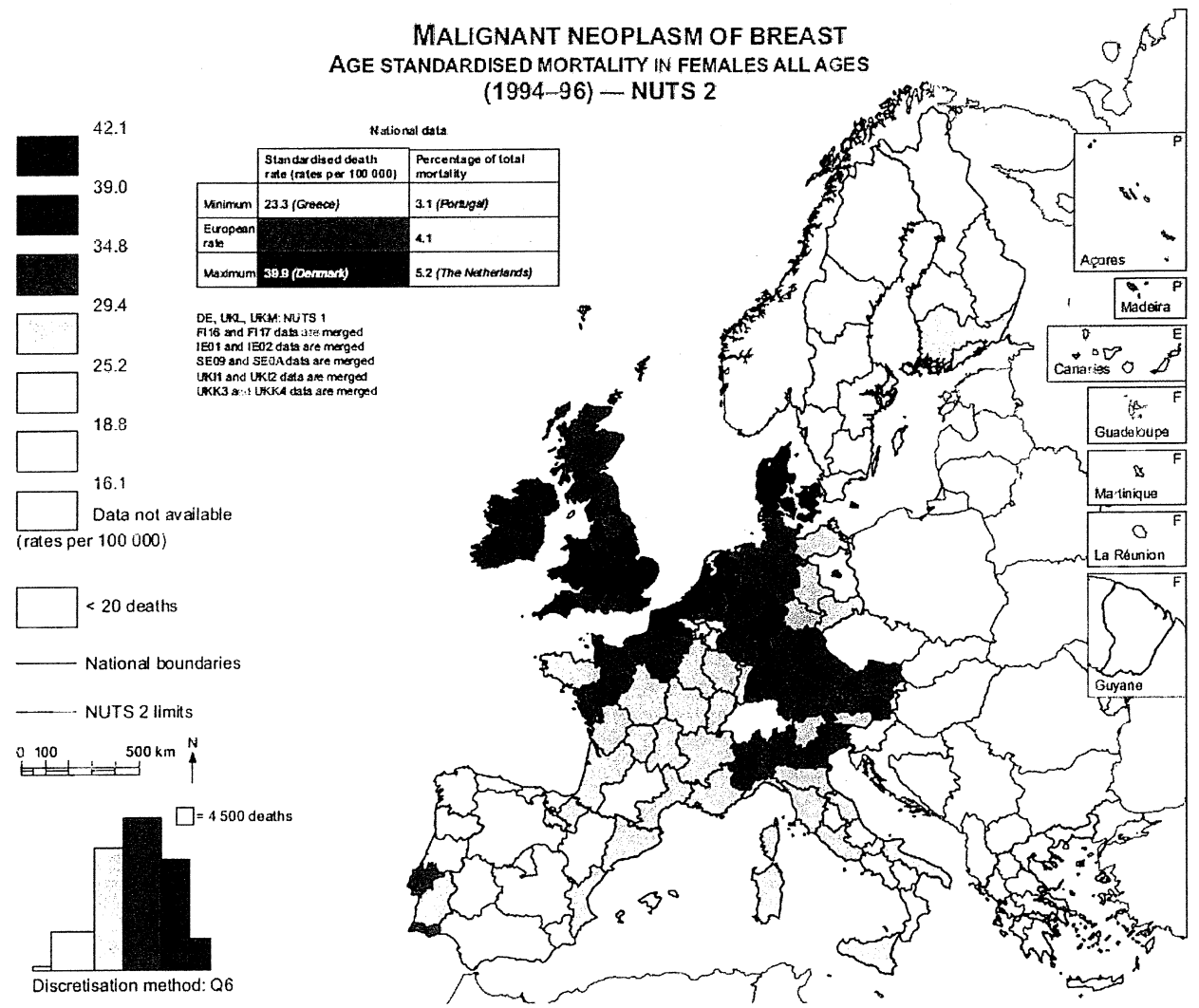
- Malignant masses
  - Hard
  - Painless: Malignant masses are painful in only 10-15% of patients.
  - Irregular
  - Possibly fixed to the skin or chest wall
  - Skin dimpling
  - Nipple retraction
  - Bloody discharge
- Benign masses
  - Firm, rubbery mass
  - Frequently painful
  - Regular margins
  - Not fixed to skin or chest wall, mobile
  - No skin dimpling
  - No nipple retraction
  - No bloody discharge
- Cysts: No reliable features distinguish cysts from solid masses based on clinical data.

Nipple discharge may be spontaneous or induced, unilateral or bilateral, and have different colors and textures. If the discharge is associated with one or more of the suggestive features, further investigation is necessary. Clinical characteristics of nipple discharges are as follows:

- Malignant discharge
  - Unilateral
  - Spontaneous
  - One duct orifice
  - Bloody, serosanguineous, or serous
- Benign discharge
  - Bilateral
  - Spontaneous or induced
  - Multiple duct orifices
  - Thick green or yellow, induced and bilateral (duct ectasia)

3. BREAST CANCER STATISTICS

Breast cancer is the most common type of cancer to affect women. It accounts for over 4 % of deaths among the female population of Europe and often affects young women: over half the number of deaths occur before 65 years. This pathology is the main cause of mortality in women aged between 45 and 64 (over 12 % of deaths). Although there are clear-cut differences in the geographical pattern of female mortality from breast cancer, it should be noted that the differences in mortality across Europe are considerably less pronounced than other cancers, particularly cancers of the respiratory tract or the upper aero digestive tract. The range of mortality compared with that of these cancers is small, at a ratio of 1 to 2.6.



Picture 2

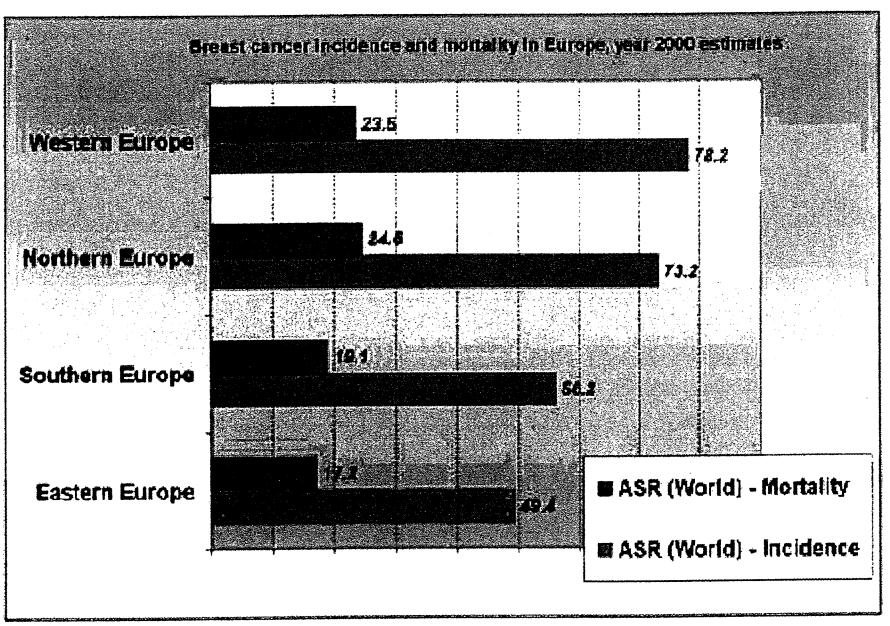
A clear-cut geographical pattern

The regional maps showing the incidence of breast cancer, which is similar at all ages and before 65 years, reveals that the spatial distribution of rates is not random and that there are continuities. A broad band of excess mortality comprises Denmark, with the highest rates in Europe, Belgium, western Germany, north-west France, northern Italy, Luxembourg, the Netherlands, Austria and the UK. In the rest of the EU, the rates are considerably lower, particularly in Greece, Spain, Finland and Sweden. In Portugal, there is a clear north/south divide, with the northern regions more favorably placed. The Mediterranean islands of Corsica, Sardinia, Sicily and the Balearics (but not the Greek islands) have similar fairly high rates, so that they are not as well placed as their respective countries. Apart from Germany, France, Italy and Portugal, where there are marked regional contrasts, the distribution of mortality from breast cancer is determined, on the whole, by national trends.

In year 2000 the regions of highest incidence are Western and Northern Europe, while Southern and Eastern Europe have lower incidence rates. The risk of getting breast cancer in Western Europe is 60% greater than in Eastern Europe. The highest mortality rates are also observed in Northern and Western Europe. The estimates for individual countries for the year 2000 show the highest incidence rates in the Netherlands (91.6/105), Denmark (86.2/105), France (83.2/105), Belgium (82.2/105), and Sweden (81.0/105). The lowest rates in Europe are observed in Macedonia (38.7/105), Lithuania (39.8/105), Belarus (39.8/105), Latvia (42.2/105), and Estonia (45.4/105).

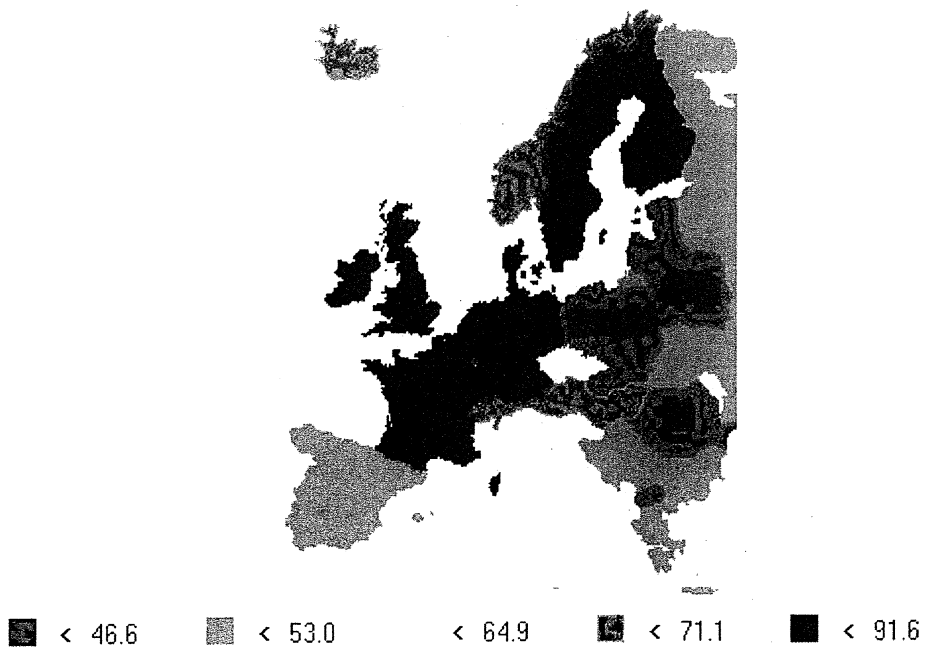
Temporal Changes in Breast Cancer in Europe

Increasing trends of breast cancer mortality were observed in European countries in the 1950s and 1960s. Deceleration of the increase in mortality or the beginning of a decline was observed in the 1970s and 1980s in several Western European countries (and also in the United States, Canada, and Australia).However, in some countries (mainly in Eastern and Southern Europe) the increase of mortality continued in the 1970s and following decades.



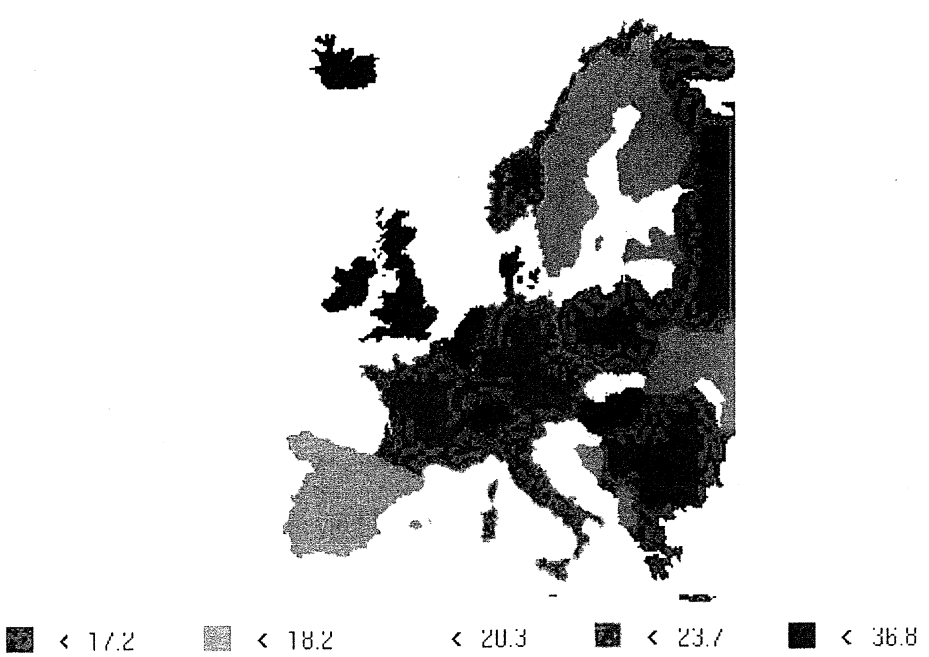
Graph 1

Incidence of breast cancer: ASR (World) (All ages), Europe 2000

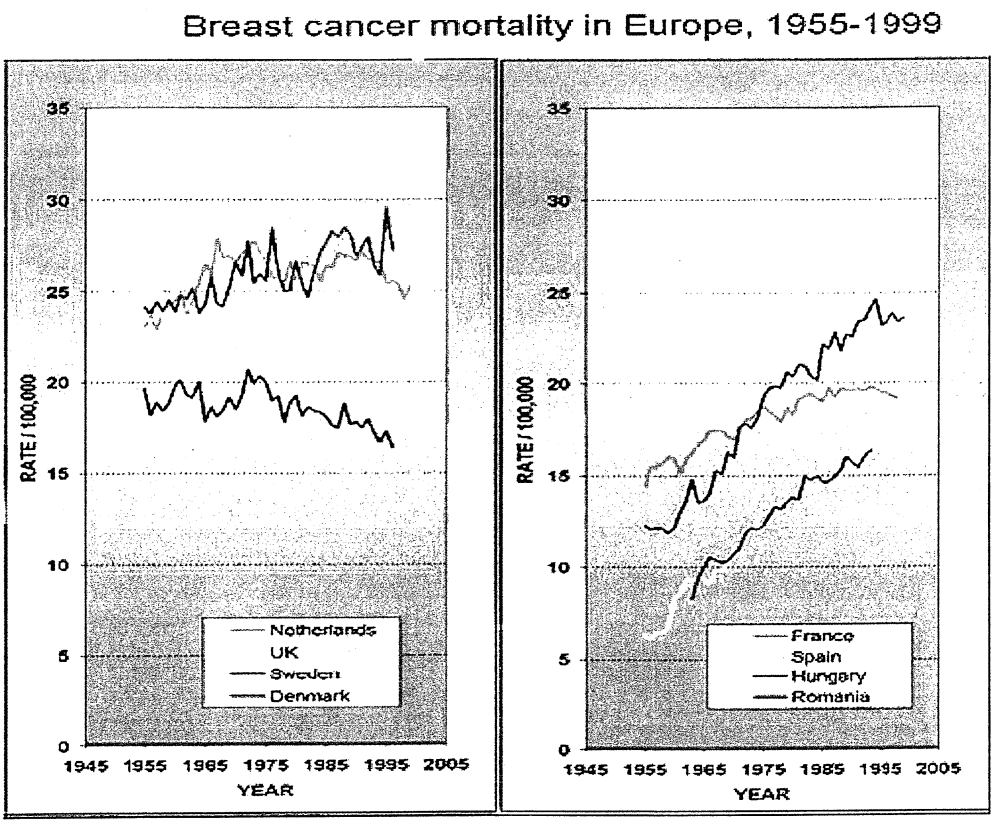


Graph 2

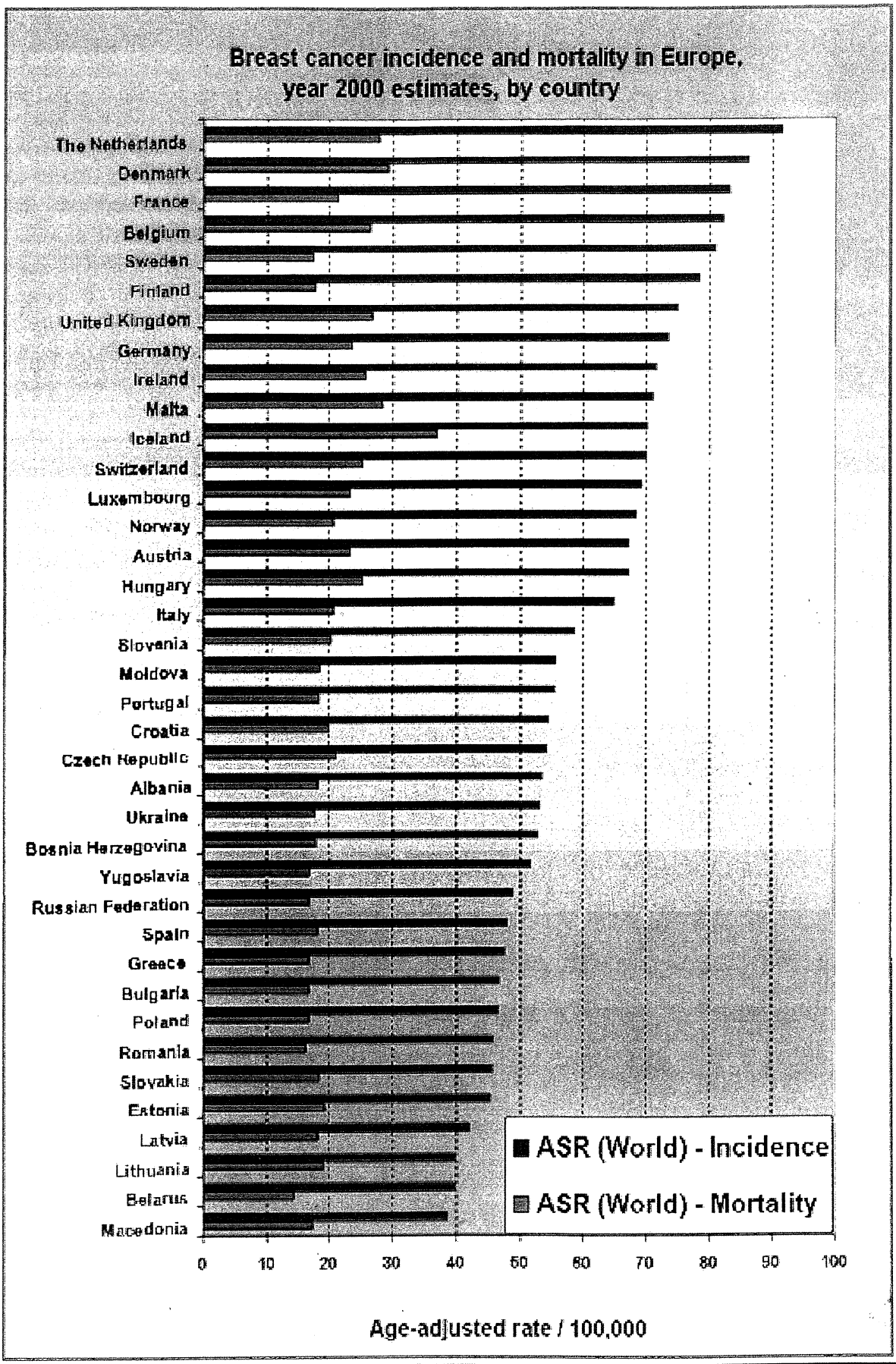
Mortality from breast cancer: ASR (World) (All ages), Europe 2000



Graph 3


Breast cancer mortality in Europe, 1955-1999
RATE / 100,000
YEAR
1945 1955 1965 1975 1985 1995 2005
0 5 10 15 20 25 30 35
Netherlands
UK
Sweden
Denmark
France
Spain
Hungary
Romania

Graph 4


Breast cancer incidence and mortality in Europe, year 2000 estimates, by country
The Netherlands
Denmark
France
Belgium
Sweden
Finland
United Kingdom
Germany
Ireland
Malta
Iceland
Switzerland
Luxembourg
Norway
Austria
Hungary
Italy
Slovenia
Moldova
Portugal
Croatia
Czech Republic
Albania
Ukraine
Bosnia Herzegovina
Yugoslavia
Russian Federation
Spain
Greece
Bulgaria
Poland
Romania
Slovakia
Estonia
Latvia
Lithuania
Belarus
Macedonia
ASR (World) - Incidence
ASR (World) - Mortality
0
10
20
30
40
50
60
70
80
90
100
Age-adjusted rate / 100,000

Graph 5

4. RISK FACTORS

A family history of breast cancer in a first-degree relative (parent, sibling, child) doubles or triples a woman's risk of developing the disease, but a history in more distant relatives increases the risk only slightly. In some studies, the risk was higher in women with relatives who had bilateral breast cancer or whose cancer was diagnosed before menopause. When two or more first-degree relatives have breast cancer, the risk may be 5 to 6 times higher. About 5% of women with breast cancer carry one of the two breast cancer genes, *BRCA1* or *BRCA2*. If a relative of such women also carries the gene, she has an increased risk of developing breast cancer. Men who carry *BRCA2* also have an increased risk of developing breast cancer. The magnitude of risk is still uncertain but may be as high as 50 to 85% by age 80. However, women with *BRCA1* or *BRCA2* do not appear to have a greater risk of dying of breast cancer after it is diagnosed than women without the gene. Women with *BRCA1* have a similarly high risk of developing ovarian cancer. Women who do not have a family history of breast cancer in at least two first-degree relatives probably do not carry this gene.

Women with a history of in situ or of invasive breast cancer are another high-risk group. The risk of developing cancer in the contralateral breast after mastectomy is about 0.5 to 1.0%/yr. Early menarche, late menopause, or late first pregnancies are also factors that increased risk. Women with a first pregnancy after age 30 are at higher risk than those who are nulliparous. A history of fibrocystic complex increases risk, but this condition is an imprecise histologic diagnosis, often assigned when a breast biopsy reveals a few cysts with normal breast tissue or very minimal proliferation; therefore, the diagnosis has little meaning. Among women who have had a biopsy for a benign breast disorder, the increased risk appears to be limited to those with ductal proliferation, and even then, the risk is moderate except for women with atypical hyperplasia. For those with atypical hyperplasia and a positive family history in a first-degree relative, the risk is increased nearly ninefold. Women with multiple breast lumps but no histologic confirmation of a high-risk pattern should not be considered at high risk.

Women who use oral contraceptives have a very small increase in their risk of developing breast cancer; about 5 more cases of breast cancer per 100,000 occur among women who use oral contraceptives. The increased risk occurs primarily during the years when women are taking the contraceptives and tapers off during the 10-yr period after they stop. The risk is also related to the age at which contraceptives are begun. Women who begin to use contraceptives before age 20 have the greatest proportional increase in the risk of developing breast cancer, although this risk is still very low.

Similarly, the use of postmenopausal estrogen replacement therapy appears to increase the risk modestly, especially after 10 to 20 years of use. However, even with prolonged use, the risk is increased less than twofold. Use of a cyclic or continuous estrogen-progestin regimen also results in a modest increase in the risk of breast cancer. Selective estrogen-receptor modulators may be able to prevent heart disease and osteoporosis and treat hot flushes with no effect on the breast.

Environmental factors, such as diet, may play a role in causing or promoting the growth of breast cancers. Obese postmenopausal women are at increased risk. Radiation exposure before age 30 also increases risk.

Table: 1

Age (yr)	Risk of Developing (or Dying of*) Breast Cancer (%)		
	In 10 yr	In 20 yr	In 30yr
30	0.4 (0.1)	2.0 (0.6)	4.3 (1.2)
40	1.6 (0.5)	3.9 (1.1)	7.1 (2.0)
50	2.4 (0.7)	5.7 (1.6)	9.0 (2.6)
60	3.6 (1.0)	7.1 (2.0)	9.1 (2.6)
70	4.1 (1.2)	6.5 (1.9)	7.1 (2.0)

* Percentage for dying of equals that for developing divided by 3.5

Based on Feuer EJ. Wun LM. Et al: "The Lifetime Risk of Developing Breast Cancer." Journal of the National Cancer Institute 85(11): 892-897. 1993

5. PREVENTION OF BREAST CANCER

Prevention of breast cancer is achieved by recognizing the risk factors in each patient and try to minimize them accordingly. All women, regardless of risk group, should be encouraged to get more informed about the risks of breast cancer and its impact in order to adopt a healthy lifestyle, with moderate exercise, limited fat and alcohol intake, no smoking, and maintenance of healthy body weight.

Selective Estrogen Receptor Modulators (SERMS) for Prevention of Breast Cancer

SERMs are drugs that act like estrogen on some tissues in the body such as bones, but block the effect of estrogen on other tissues. The selective estrogen receptors modulators (SERMs) were initially developed as antistrogens for the treatment of breast cancer, but their unusual properties have led to their use in the treatment and prevention of other diseases as well. SERMs bind the estrogen receptor (ER) and modulated ER-mediated gene transcription.

Despite the beneficial effects of estrogens in women's health, there is a plethora of evidence that suggest an important role for these hormones, particularly 17beta-estradiol (E(2)), in the development and progression of breast cancer. Most estrogenic responses are mediated by estrogen receptors (ERs), either ERalpha or ERbeta, which are members of the nuclear receptor superfamily of ligand-dependent transcription factors. Selective estrogen receptor modulators (SERMs) are ER ligands that in some tissues (i.e. bone and cardiovascular system) act like estrogens but block estrogen action in others. Numerous studies have examined the molecular mechanisms for the tissue selective action of SERMs, and collectively they indicate that different ER ligands induce distinct conformational changes in the receptor that influence its ability to interact with coregulatory proteins (i.e. coactivators and corepressors) critical for the regulation of target gene transcription. The relative expression of coactivators and corepressors, and the nature of the ER and its target gene promoter also affect SERM biocharacter. This review summarizes the therapeutic application of SERMs in medicine; particularly breast cancer, and highlights the emerging understanding of the mechanism of action of SERMs in select target tissues, and the inevitable development of resistance.

Tamoxifen is the first SERM that has been successfully tested for the prevention of breast cancer in high-risk women and is currently approved for the endocrine treatment of all stages of ER-positive breast cancer. It blocks the effect of estrogen on breast cancer cells. It reduces the annual odds of death by about 25% in premenopausal and postmenopausal women and in women with or without axial lymph node involvement. It also decreases the incidence of contralateral breast cancer and serum cholesterol. Tamoxifen has almost no acute adverse effects in postmenopausal but it can cause endometrial cancer, deep venous thrombosis and pulmonary embolism in other cases. Tamoxifen is an effective treatment for hormone responsive breast cancer and can prevent breast cancer in high-risk women.

Raloxifene is a newer SERM originally developed for osteoporosis, but also appears to have preventive effect on breast cancer incidence. Studies of postmenopausal women with osteoporosis has shown that raloxifene lowered the risk of breast cancer for women at both high risk and low risk of developing the disease. It is not known if women who do not have osteoporosis would benefit in the same way. Like tamoxifen, raloxifene may increase the risk of blood clots in veins and in the lungs, but does not appear to increase the risk of endometrial cancer. Raloxifene was approved for the prevention and treatment of osteoporosis in postmenopausal women, also appears to prevent breast cancer.

Biochemical actions of Tamoxifen and Reloxifene

The most important aspects of these therapies are focused on their influence on bone and lipid metabolism. Several studies have reported the effect of tamoxifen and raloxifene on plasma lipids. Tamoxifen therapy significantly reduces the excretion of taurocholic acid and glycochenodeoxycholic plus glycodeoxycholic acids, and excretion of cholic, litocholic and chenodeoxycholic plus deoxycholic acids was increased. Raloxifene significantly reduces the excretion of taurocholic, glycocholic and litocholic acids, taurochenodeoxycholic plus taurodeoxycholic acids, as well as chenodeoxycholic plus deoxycholic acids.

Melatonin

Several reviews on experimental data support an oncostatic role of melatonin on hormone-dependent mammary tumors. Melatonin fulfills all the requirements to be considered as an antiestrogenic drug which shares properties with drugs of the two main pharmacological groups of substances which interact with the estrogen-signaling pathways such as: (i) drugs that act through the estrogen receptor interfering with the effects of endogenous estrogens; and (ii) drugs that interfere with the synthesis of estrogens by inhibiting the enzymes controlling the interconversion from their androgenic precursors. Furthermore, melatonin decreases circulating levels of estradiol. These three antiestrogenic mechanisms suggest that melatonin may have an important role in the prevention and treatment of hormone-dependent mammary cancer.

Hormonal Factors: Hormones produced by the ovaries appear to increase a woman's risk for developing breast cancer. The removal of one or both ovaries reduces the risk. The use of drugs that suppress the production of estrogen may inhibit tumor cell growth. The use of estrogen-progestin therapy, also called combination hormone replacement therapy (HRT), is associated with an increased risk of developing breast cancer and this risk may rise in women who use HRT beyond five years. Further, women entering menopause may sometimes receive concomitant oral contraceptives and HRT, which was shown in one study to triple the risk of breast cancer compared with that in women who did not use either agent. The use of oral contraceptives may also be associated with a slight increase in breast cancer risk; a slightly elevated risk of breast cancer persisted for up to 10 years after cessation of oral contraceptives, but the risk was not significantly greater beyond that time. Notably, though, tumors diagnosed in women who were using or had used oral contraceptives were generally less advanced clinically than those diagnosed in women who had never used oral contraceptives.

Alpha-Fetoprotein (AFP)[40] is a protein of pregnancy associated with a decrease in lifetime risk of breast cancer in parous women. This was proved by Parikh RR and his team who developed a synthetic, cyclic nonapeptide developed that mimics the antioncogenic active site of AFP. To test the hypothesis that the AFP-derived peptide (AFPep) can prevent breast cancer, the N-methyl-N-nitrosourea-induced breast cancer model was used in rats. According to the experimental design AFPep was given daily by injection beginning 10 days after N-methyl-N-nitrosourea treatment and continued for 23 days (a time designed to mimic pregnancy) or for other times to assess efficacy as a function of drug duration. Tumor incidence, multiplicity, and latency were noted as end points. At necropsy, pathology analysis of tumors and major organs were obtained. As it was proved AFPep prevented cancer in a dose-dependent fashion. Significantly longer mean tumor-free days ($P < 0.02$), lower tumor incidence ($P = 0.004$), and lower tumor multiplicity were observed for AFPep-treated groups. No evidence of host toxicity as measured by body weight, cage activity, fur texture, and organ weights (liver, uterus, heart, kidney, and spleen) were found in animals treated with AFPep. Mechanistic studies using transplantable human breast cancer xenografts showed that the peptide interfered with estrogen-dependent breast cancer growth inhibited the phosphorylation of the estrogen receptor and activated phosphorylation of p53.

Menarche and Menopause: Most breast cancer risk factors relate to gynecological or endocrinological events in a woman's life. Age at menarche is related to a woman's chance of developing breast cancer, compared with women who experience menarche at age 16, girls who experience menarche two to five years earlier have a 10% to 30% greater risk of developing breast cancer later in life. A similar observation has been made for the timing of events at the other end of the reproductive spectrum, the age at menopause. If we use women who experience menopause between the ages of 45 and 55 years as the referent group, women who experience menopause at age 55 or older have a 50% higher risk of subsequently developing breast cancer, and women who cease menstruating at age 45 or younger have a 30% lower risk of subsequently developing breast cancer. These data, along with the observations about the age at menarche, indicate that one way of expressing the risk of breast cancer in relation to gynecological events is simply to count the number of ovulatory menstrual cycles that a woman experiences in her lifetime. Early menarche and late menopause lead to an increased total lifetime number of menstrual cycles and a corresponding 30% to 50% increase in breast cancer risk. Conversely, late menarche and early menopause lead to a reduction in breast cancer risk of similar magnitude. Consistent with this observation is the fact that oophorectomy before the age of menopause (especially before the age of 40) lowers the risk of breast cancer by approximately two thirds.

Pregnancy: Pregnancy at a young age, especially before the age of 20, markedly reduces the incidence of subsequent breast cancer. Conversely, both nulliparity and age older than 30 at first live birth are associated with nearly a doubling of the risk of subsequent breast cancer. Pregnancies not ending in the birth of a viable fetus do not confer reduction in the risk of breast cancer.

Surgical Risk Reduction (Prophylactic Mastectomy): Bilateral prophylactic mastectomy is the most certain means of reducing breast cancer risk. Nevertheless, because breast tissue is widely distributed over the entire anterolateral portion of the chest wall and axilla, no mastectomy can remove all existing mammary tissue Prophylactic mastectomy is associated with a reduction in the incidence of breast cancer of at least 90%. Prophylactic mastectomy has been described as a disfiguring and potentially psychologically damaging operation. As such, it should be considered carefully, particularly as less invasive therapies become available. Possible indications for prophylactic mastectomy include a strong family or personal history of breast cancer, multiple previous breast biopsies, unreliable results on physical examination because of nodular disease, findings of dense breast tissue on mammography, mastodynia, and cancerphobia.

Radiation Exposure: Relatively low doses of radiation (less than 0.2 Gy) have been associated with an increased incidence of solid tumors such as breast cancer. Women who have undergone chest wall irradiation therapy—as treatment for Hodgkin's disease, for example- during childhood or adolescence have a significantly increased risk for breast cancer. It is important to note, however, that the very low doses of radiation associated with screening mammography do not increase the risk of breast cancer appreciably in individual women.

Alcohol Consumption: Alcohol consumption, like dietary fat intake, has been a controversial topic in breast cancer research. There are several mechanisms by which ethanol may increasethe risk of breast cancer. It may (1) induce increased levels of circulating estrogen; (2) stimulate hepatic metabolism of carcinogens such as acetaldehyde; (3) facilitate transport of carcinogens into breast tissue; (4) stimulate pituitary production of prolactin; (5) modulate cell membrane integrity with an effect on carcinogenesis; (6) aid production of cytotoxic protein products; (7) impair immune surveillance; (8) interfere with DNA repair; (9) promote production of toxic congeners; (10) increase exposure to toxic oxidants; and/or (11) reduce intake and bioavailability of protective nutrients. Few of these mechanisms have been studied, however, either in experimental animals or humans. Alcohol consumption has, however, been linked to higher serum estrogen levels: Women with consistently high estradiol levels have a significantly higher average alcohol intake (92.8 g/wk) than those with consistently lower estradiol levels (alcohol intake, 31.6 g/wk).

Genetics: Not more than 10% of human breast cancers can be linked directly to germline mutations. Several genes have been implicated in familial cases. The Li-Fraumeni syndrome is characterized by inherited mutations in the p53 tumor suppressor gene, which lead to an increased incidence of breast cancer, osteogenic sarcomas, and other malignancies. The p53 mutation is present in approximately 40% of human breast cancers as an acquired defect

Another putative tumor suppressor gene, BRCA-1, has been identified at the chromosomal locus 17q21; this gene encodes a zinc finger protein, and the product therefore may function as a transcriptional factor. The gene appears to be involved in gene repair. Women who inherit a mutated allele of this gene from either parent have an approximately 60 to 80% lifetime chance of developing breast cancer and about a 33% chance of developing ovarian cancer. Evidence for BRCA-1 mutation in primary breast cancer has not been reported. However, decreased expression of BRCA-1 mRNA and abnormal cellular location of the BRCA-1 protein have been found in some breast cancers. Loss of heterozygosity of some genes suggests that tumor-suppressor activity may be inactivated in sporadic cases of human breast cancer. Finally, one dominant oncogene plays a role in about a quarter of human breast cancer cases. The product of this gene, a member of the epidermal growth factor receptor superfamily, is called erbB2 (HER-2, neu) and is overexpressed in these breast cancers due to gene amplification; this overexpression can transform human breast epithelium. Men who carry a mutant allele of the gene have an increased incidence of prostate cancer but usually not of breast cancer. A third gene, termed BRCA-2, which has been localized to chromosome 13q12, is associated with an increased incidence of breast cancer in men and women. BRCA-1 and BRCA-2 can now be sequenced readily and germline mutations detected; patients with these mutations can be counseled appropriately. All women

with strong family histories for breast cancer should be referred to genetic screening programs whenever possible, particularly women of Ashkenazi Jewish descent who have a high likelihood of a specific BRCA-1 mutation (deletion of adenine and guanine at position 185).

In 1995 scientists from the National Institutes of Health (NIH) discovered that a particular alteration in the breast cancer gene called BRCA1 was present in 1 percent of the general Jewish population. The researchers did a follow-up study in 1996 to estimate the cancer risk associated with this alteration as well as two other alterations subsequently reported to be present in the Ashkenazi Jewish population.

The primary purpose of the study was to estimate the risk of cancer associated with having three specific alterations in the breast cancer genes, BRCA1 and BRCA2. The study was conducted in the Washington, D.C. Ashkenazi Jewish population (Jews from eastern or central Europe). Two of the alterations tested were in the BRCA1 gene (185delAG and 5382insC) and one in the BRCA2 gene (6174delT). This was the first study to test directly the DNA from volunteers who are outside cancer-prone families and estimate the cancer risk associated with each alteration. For years, researchers have studied families with breast cancer throughout several generations to help identify the altered genes passed on from one generation to the next. It was also the first community-based study where people with varying degrees of family cancer history participated. In fact, three-quarters of the volunteers had no personal or close family history of breast or ovarian cancer and 30 percent were men. About 8 percent of the women were breast or ovarian cancer survivors.

Within families with cancer in multiple generations, it had been estimated previously that a woman with an alteration in the BRCA1 gene has about an 85 percent chance of developing breast cancer and a 44 percent chance of developing ovarian cancer by age 70. Prior research in these high-risk families reported that women with BRCA2 alterations have a lower risk of developing both breast and ovarian cancer than women with BRCA1 alterations. Previous studies had reported an increased risk of colon and prostate cancer associated with alteration carriers in these same families. Most alterations result in a shortened protein product which scientists assume prevents the protein from carrying out its normal function in the cell. Once the genes were isolated, it was possible to analyze the specific alterations inherited in each cancer-prone family. Today over 100 different alterations scattered throughout BRCA1 have been identified. In general, most families have a unique alteration. A similar pattern is emerging for BRCA2 alterations seen in cancer-prone families; a large number of distinct, family-specific alterations are scattered through the gene. This observation led to the study which found that 1 percent of the Jewish population has this alteration. This was the first alteration associated with a particular ethnic group. In particular, three alterations were initially identified in Ashkenazi families with hereditary breast cancer and later were found in an unusually high percentage of the general Jewish population. The estimated frequencies of the three alterations in the general Ashkenazi population are listed below:

Gene	Alteration	Frequency in Ashkenazi Jews*
BRCA 1	185delAG	1.0 percent
	5382insC	0.1 percent
BRCA2	6174delT	1.4 percent

On average, by the age of 70, women with one of the alterations tested for in this study have about a 50 percent chance of being diagnosed with breast cancer and 16 percent chance of developing ovarian cancer. Men with an alteration have about a 16 percent chance of developing prostate cancer by the age of 70. However, for any individual with an alteration, a precise estimate of risk is not possible. Family history helps to place an individual's cancer risk in perspective, but is also an imperfect tool. For example, family history will be most useful in determining risk if a carrier has multiple relatives affected with breast or ovarian cancer. In this case, a woman's risk of breast cancer may be higher than the average of 56 percent. If a carrier has little or no family history of breast and ovarian cancer, his or her risk will be much more difficult to assess. This is particularly true of women in small families with very few close female relatives. Unless someone already has a strong family history of breast or ovarian cancer, it will be very difficult to know his or her precise risk until other risk factors for cancer are identified.

Diet:

Breast cancer is perhaps the most intensively studied human neoplasm with respect to its possible nutritional causes. Most epidemiologic studies have not found a relationship between dietary fats and breast cancer, yet the hypothesis is currently being tested as part of the Women's Health Initiative, a large trial in which thousands of women have been randomly assigned to a mixed dietary intervention that features, among other things, a diet that derives between 20% and 25% of calories from fat. The results of that trial will not be known for several more years. A stronger relationship than that with dietary fat has been seen between breast cancer and alcohol, yet the effects of alcohol cannot easily be tested in a randomized controlled trial, both because alcohol has adverse effects in excess and in lower doses and because alcohol is also associated with cardiovascular benefits. Although fruits and vegetables have been associated with lower breast cancer risk in many observational studies, the degree of that association is less than that for colon or lung cancers. Moreover, individuals who report eating few fruits and vegetables also report other health-related risk factors, including greater levels of body weight, higher alcohol use, and less physical activity—factors that could together confound the weak relationship with fruits and vegetables. Some have proposed that breast cancer risk may be modified by the phytoestrogenic compounds found in certain fruits and vegetables. According to that hypothesis, the beneficial endocrine effects of these compounds, together with essential vitamins and minerals, might account for reduced breast cancer risk. Recent findings regarding tamoxifen and reduced breast cancer risk have further fuelled interest in any natural antistrogens that can be obtained from foods. Soybean products that contain high levels of phytoestrogens have been of particular interest.Although it is possible that these plant foods could reduce breast cancer risk because they act as antiestrogens, it is equally possible that soy, when taken in high doses, exerts pro-estrogenic effects, especially among postmenopausal women, resulting in increased cancer incidence among women carrying estrogenreceptor positive breast tumors. Hopefully, the uncontrolled experimentation that is now underway among breast cancer survivors taking high-dose soy will not result in the same sort of disturbing surprise found by the randomized clinical trials of high-dose beta carotene.

Worldwide, each year approximately one million women are newly diagnosed with breast cancer, in Germany 65 new cases per 100,000 inhabitants are registered, yearly. The fact that incidence has been rising in parallel with economic development indicates that environmental factors might play a role in the causation of breast cancer. Migrational data have pointed to nutrition as one of the more relevant external factors involved. Preventive dietary advice often includes a reduction of alcohol, red meat and animal fat and increasing the intake of vegetables, fruit and fibre and lately, phytoestrogens from various sources. Clearly, the scientific basis for these recommendations appears sparse. The available prospective data from epidemiological studies and interventional trials do not support the overall hypothesis that higher fat-intakes are a relevant risk factor for breast cancer development, more important seems the relative distribution of various fatty acids. A non-vegetarian eating habit (consumption of animal products) per se does not elevate breast cancer risk, while consumption of broiled or deep fried meats cannot be ruled out as a risk factor in genetically susceptible individuals. It appears prudent to abstain from regular and increased alcohol consumption. This should be particularly true for pubescent girls, in whom glandular breast tissue is particularly vulnerable. In general, if alcohol is consumed on a regular basis, a sufficient supply of fresh vegetables and fruit is essential. While there is no overall protective effect of a high fruit and vegetable consumption speculation remains over possible beneficial effects of certain subcategories, especially brassica vegetables like broccoli, cauliflower and cabbage. In essence, regional differences in breast cancer incidence are probably partially attributable to life long dietary habits. There is no need to adopt a foreign dietary plan in order to protect oneself against breast cancer. Traditional western diets also have their beneficial ingredients that should be regular constituents in our meals. Lignans from traditionally made sourdougrye bread, linseed/flaxseed and berries are local sources of potentially canceroprotective phytoestrogens. Furthermore, indole-3-carbinol rich cabbage species might contribute to breast cancer protection by diet. Nevertheless, clear cut recommendations for or against single nutrients or secondary plant metabolites are not yet possible, lacking sufficient data on individual bioavailability, safety and long term outcome. breast cancer prevention by dietary means therefore relies on an individually tailored mixed diet, rich in basic foods and traditional manufacturing and cooking methods.

The strongest evidence linking specific foods to decrease risk of certain cancers includes the consumption of fruits and vegetables and whole grains. Secondary prevention trials and observational prospective epidemiologic studies have demonstrated the efficacy of a Mediterranean-type dietary pattern to

decrease risk of both cancer and cardiovascular diseases. We recommend the adoption of dietary patterns emphasizing regular physical activity, fruits and vegetables, whole grains, legumes, nuts, seeds, and low-fat dairy products to all people at risk for cancer and cardiovascular disease. These recommendations may be incorporated into enjoyable cultural food patterns as exemplified by Mediterranean-type diets. The preparation and enjoyment of meals in a convivial atmosphere is a vital component of lifestyles to prevent chronic diseases such as cancer and certain cardiovascular diseases.

Of a particular interest is retinoic acid and its synthetic analogs exert major effects on many biological processes including cell proliferation and differentiation and are now considered as promising pharmacological agents for prevention and treatment of various cancers. The capacity of retinoids to inhibit AP1-responsive genes seems to be the basis for the chemopreventive and chemotherapeutic effects of these agents against hyperproliferative diseases. However, the molecular basis of retinoid antiproliferative properties remains to this day largely unknown. Here, we showed that retinoids inhibit phorbol ester-induced MMP-1 and MMP-3 expression in human breast cancer cells. Transcriptional interference was observed for both retinoid agonist and antagonist treatments, revealing separated transactivation and transrepression functions of retinoids. In addition, we examined MAP kinases as potential targets of retinoid signalling in human breast cancer cells and demonstrated that retinoids repress AP1-responsive gene expression by inhibiting MKK6/p38 and mainly MEK/ERK signalling pathways. On the contrary, the JNK-dependent pathway was not identified as a molecular relay for AP1 activity and was insensitive to retinoid treatments. Finally, we established that overexpressed c-fos and c-jun partially abolished the ability of retinoids to inhibit AP1 activity, suggesting that c-jun and/or c-fos containing dimers may constitute one target of retinoids for transrepression of AP1. All together, our data help to improve our understanding of how retinoids antagonize AP1 activity and may regulate tumoral cell proliferation.

Prenatal Reasons[41]

The recognized role of perinatal nutrition in neurologic development and the relation of maternal nutritional status to birthweight and subsequent risk of hypertension, diabetes, and cardiovascular disease identify pregnancy and early childhood as potential phases for prevention. Forman MR, and his collegues in their review examined indicators of hormonal and nutritional exposures in early life and breast cancer risk through the lens of the life course paradigm integrated with maternal and child health research and methodology. Compared to women who were normal birthweight (2500-3999 g), women who weighed >/= 4,000 g at birth have a 20 percent to 5-fold increased risk of premenopausal breast cancer. Women born preterm and likely to be small- or large-for-date also have an increased risk. Birth length is directly associated with risk and has a larger magnitude of effect than birthweight. Prior preeclamptics and their daughters have a lower risk of breast cancer than comparable normotensives. An association between infant feeding practices and breast cancer is unclear without improved exposure assessment and analysis. Rapid childhood and pubertal linear growth increases breast cancer risk, while greater body fat over the same periods reduces risk. Growth data thus far have not been calculated in Z-scores from reference growth curves for comparison across studies. Events and secular trends influencing birth cohorts may not be adequately addressed, thereby limiting the interpretation and implications of the findings.

Smoking

Cigarette smoking has been shown to increase the risk of lung and other types of cancer and to increase the risk of heart disease. Smoking affects overall health and may increase risk for breast cancer, but no controlled trials have thus far established a definite link between smoking and breast cancer

Exercise

Exercise may reduce breast cancer risk, but no biologic mechanism has been determined. Exercise enhances immune function, is associated with lower body fat, and affects hormonal levels, all of which may affect breast cancer. Confounding factors make it difficult to assess this relationship, because women who exercise regularly are also likely to smoke less, drink less, have different menstrual and reproductive patterns, and consume different diets than sedentary women. Most studies report a decreased risk of breast cancer with increasing amounts of physical activity, though a few studies found no such association.

Obesity: Obesity has been associated with an increased risk of breast cancer in postmenopausal women, which may occur because fat stores provide an important source of hormone substrates in postmenopausal women. This association is complex, though, and may change with age 59 or fat distribution. It has not been shown clinically that reducing body weight can lower breast cancer risk, but this topic deserves further study.

American Cancer Society Guidelines for Early Breast Cancer Detection, 2003

Women at Average Risk	Begin mammography at age 40. For women in their 20s and 30s, it is recommended that clinical breast examination be part of a periodic health examination, preferably at least every three years. Asymptomatic women aged 40 and over should continue to receive a clinical breast examination as part of a periodic health examination, preferably annually. Beginning in their 20s, women should be told about the benefits and limitations of breast self-examination (BSE). The importance of prompt reporting of any new breast symptoms to a health professional should be emphasized. Women who choose to do BSE should receive instruction and have their technique reviewed on the occasion of a periodic health examination. It is acceptable for women to choose not to do BSE or to do BSE irregularly. Women should have an opportunity to become informed about the benefits, limitations, and potential harms associated with regular screening.
Older Women	Screening decisions in older women should be individualized by considering the potential benefits and risks of mammography in the context of current health status and estimated life expectancy. As long as a woman is in reasonably good health and would be a candidate for treatment, she should continue to be screened with mammography.
Women at Increased Risk	Women at increased risk of breast cancer might benefit from additional screening strategies beyond those offered to women of average risk, such as earlier initiation of screening, shorter screening intervals, or the addition of screening modalities other than mammography and physical examination, such as ultrasound or magnetic resonance imaging. However, the evidence currently available is insufficient to justify recommendations for any of these screening approaches.

A Model for Risk Assessment

Gail and colleagues at the National Cancer Institute have developed a statistical model to assess a woman's individualized absolute risk of developing breast cancer such as the chance that a woman with specific risk factors at a given age will develop breast cancer in a specified future time period. The risk factors used in the model are listed in Table 2. Women are considered to have a high risk for breast cancer when their risk is equal to or greater than that of the average 60-year-old woman. Validation has been demonstrated only in women undergoing regular mammographic screening. The model was also developed before genetic testing for breast cancer was common, so the accuracy of the assessment in women with genetic predisposition is not known. This model has been validated, however, in a recent prospective study of women who were at risk of developing breast cancer.

Factors Used in the National Cancer Institute's Model to Determine the Risk of Breast Cancer

- Current age
- Race
- Age at menarche
- Age at first live birth (or nulliparity)
- Number of breast biopsies
- Atypical hyperplasia
- Number of first-degree relatives with breast cancer (ie, mother, sisters, daughters)

Breast cancer can spread insidiously. At diagnosis, 5% to 15% of patients have metastatic disease and almost 40% more have had regional spread of the disease. Further, among those with only local tumors at diagnosis, 24% to 30% will experience relapse. As treatment is sometimes unsuccessful or may be started too late, preventing cancer is preferable. Further, preventing breast cancer with safe, well-tolerated drugs is clearly preferable to treatment with radiation and cytotoxic chemicals that have significant, and often distressing, side effects. Currently, two approaches have been proven to decrease breast cancer incidence: Prophylactic mastectomy and preventive therapy with tamoxifen. Surgery provides the greater risk reduction, but because of its severe physiologic and psychological consequences, it is considered only in very high-risk cases. Pharmacologic breast cancer prevention has been associated with side effects (including increased risk of endometrial cancer) but has been shown to improve the lipid profile, preserve bone mineral density, and decrease the incidence of bone fractures to the hip, radius, and spine. Risks of both approaches must therefore be weighed carefully against potential benefits in the reduction of breast cancer risk.

Lifestyle Modifications Recommended for All Women

- Weight control
- No cigarette smoking
- Decreased alcohol consumption
- Exercise
- Avoidance of non-diagnostic, ionizing radiation

6. BREAST CANCER PREVENTION STUDIES

Breast cancer prevention studies are clinical trials that explore ways of reducing the risk, or chance, of developing breast cancer. Prevention studies usually involve women who have not had breast cancer, but are at high risk of developing the disease. Through such studies, scientists hope to determine what steps are effective in reducing the risk of breast cancer in women of all races and ethnic backgrounds.

Most breast cancer prevention research is based on evidence linking the development of this disease, in many cases, with exposure to the hormone estrogen. The focus of several recent breast cancer prevention studies has been on testing the effectiveness of drugs called selective estrogen receptor modulators (SERMs). SERMs are drugs that have some anti-estrogen properties and some estrogen-like properties. Their anti-estrogen activity may help reduce the risk of breast cancer by blocking the effects of estrogen on breast tissue. Their estrogen-like properties may help prevent the loss of bone density in postmenopausal women; however, SERMs may cause bone loss in premenopausal women.

The Breast Cancer Prevention Trial (BCPT)

The Breast Cancer Prevention Trial (BCPT) was funded by the National Cancer Institute (NCI) and conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP). The BCPT was designed to see whether tamoxifen, a SERM, can prevent breast cancer in women who are at an increased risk of developing this disease. The study began recruiting participants in April 1992 and closed enrollment in September 1997. This study involved 13,388 premenopausal and postmenopausal women at more than 300 centers across the United States and Canada. Results showed 49 percent fewer diagnoses of invasive breast cancer in women who were randomized to take tamoxifen compared with women who were randomized to take a placebo. Women on tamoxifen also had 49 percent fewer diagnoses of noninvasive breast tumors, such as ductal or lobular carcinoma in situ. Nine women died of breast cancer, three women in the tamoxifen group and six women in the placebo group. In the BCPT, most of the side effects associated with tamoxifen were temporary.

However, there were some long-term risks, including several serious health problems: endometrial cancer, uterine sarcoma, pulmonary embolism, deep vein thrombosis, and stroke. Because of these risks, women taking tamoxifen should be monitored by their doctors for any sign of serious side effects. All BCPT

participants have been asked to undergo regular follow-up examinations. BCPT participants who were randomized to the tamoxifen group and had not completed 5 years of tamoxifen therapy when the study ended were given the opportunity to continue on therapy. Postmenopausal women who had been taking the placebo were invited to participate in another trial, the Study of Tamoxifen and Raloxifene (STAR).

Breast Cancer Risk Reduction with Tamoxifen Among Various Subsets of Healthy Women

Subset	Relative Risk Reduction (%)	p Value
Overall Incidence of Invasive Breast Cancer	49	0.00001
Age Group		
< 49	44	
50-59	51	
≥ 60	55	
Lobular Carcinoma In Situ	56	
Atypical Hyperplasia	86	
Overall Incidence of Non-invasive Breast Cancer	50	0. 002
Incidence of ER-Positive Tumors	69	
Incidence of ER-Negative Tumors	0	

ER = estrogen receptor.
Adapted from Fisher B et al,[19] with permission.

The Study of Tamoxifen and Raloxifene (STAR)

The NSABP is conducting the Study of Tamoxifen and Raloxifene, known as STAR. The study is funded primarily by the NCI. The 19,000 participants are postmenopausal women who are at least 35 years old and are at increased risk for developing breast cancer. The study will determine how raloxifene, another SERM, compares with tamoxifen in reducing the incidence of breast cancer in women who are at an increased risk of developing the disease. As with tamoxifen, most of the known side effects of raloxifene are temporary. However, like tamoxifen, raloxifene increases the risk of pulmonary embolism and deep vein thrombosis.

Capital Area SERM Study

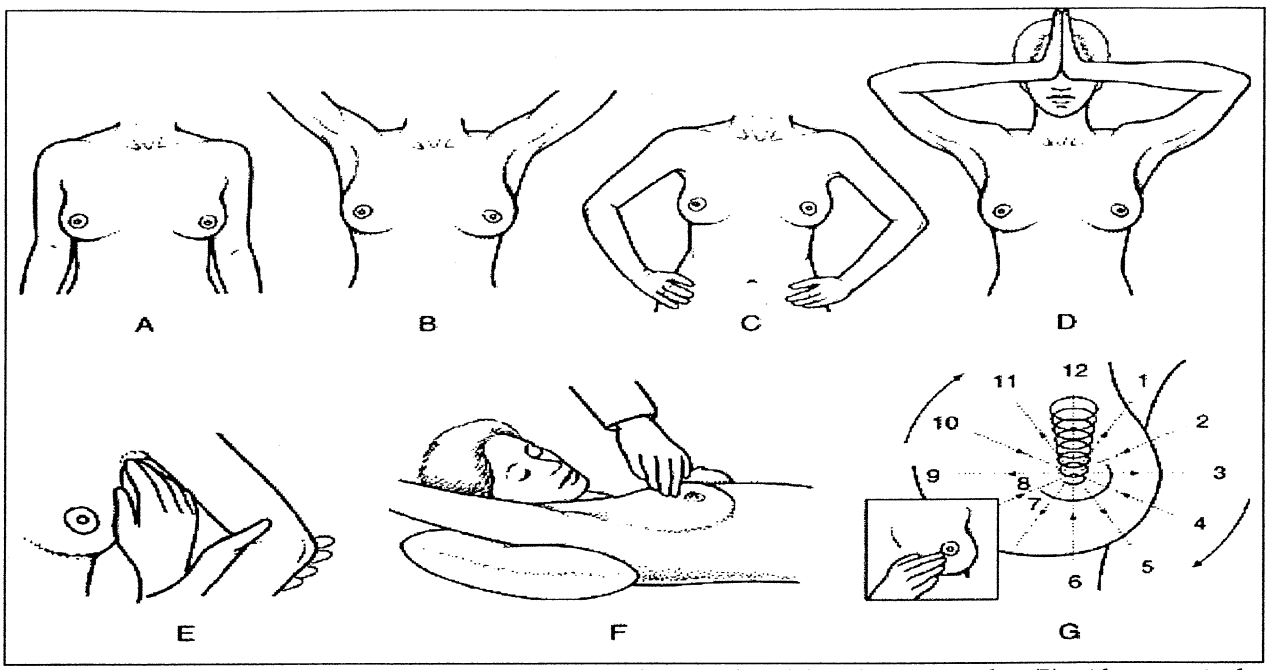
The NCI is also conducting the Capital Area SERM Study to evaluate the safety of raloxifene in premenopausal women between the ages of 23 and 47 who are at increased risk for breast cancer. Thirty-seven women enrolled in this study.

Other Breast Cancer Prevention Studies

Drugs called aromatase inhibitors, which have been approved by the U.S. Food and Drug Administration to treat hormone-sensitive breast cancer, are being studied in clinical trials for breast cancer prevention. These drugs interfere with the adrenal enzyme aromatase, which is responsible for estrogen production in postmenopausal women. The NCI is also studying prevention options for women at high risk of breast cancer that is not sensitive to hormones and can be more difficult to treat than hormone-sensitive breast cancer.

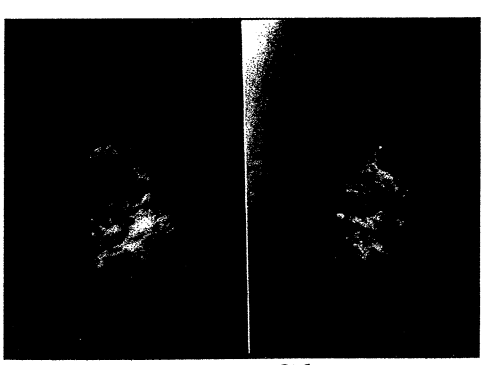
7. SCREENING

Women should be strongly encouraged to examine their breasts monthly; the minimum benefit of this practice is the greater likelihood of detecting a mass at a smaller size, when it can be treated with more limited surgery. The patient should be instructed in breast self-examination during her annual breast examination by a physician or a specially trained nurse. Breast examination by patient or physician begins with visual inspection for asymmetry in breast size, nipple inversion, bulging, or dimpling. All regional lymph node groups should be examined, and any lesions should be measured. Physical examination alone cannot exclude malignancy.



Picture 3. Positions for breast examination. Patient seated or standing (A) with arms at sides; (B) with arms raised over the head, elevating the pectoral fascia and breasts; (C) with hands pressed firmly against hips; or (D) with palms pressed together in front of the forehead, contracting the pectoral muscles. (E) Palpation of axilla; arm supported as shown, relaxing the pectoral muscles. (F) Patient supine with pillow under the shoulder and arm raised above the head on the side being examined. (G) Palpation of breast in circular pattern from the nipple outward.

In premenopausal women, lesions that are either equivocal or nonsuspicious on physical examination should be reexamined in 2 to 4 weeks, during the follicular phase of the menstrual cycle. Days 5 to 7 of the cycle are the best time for breast examination. A dominant mass in a postmenopausal woman or a dominant mass that persists through a menstrual cycle in a premenopausal woman should be aspirated by fine-needle biopsy or referred to a surgeon. If a nonbloody fluid is aspirated and the lesion is thereby cured, the diagnosis and therapy have been accomplished together. Solid lesions that are persistent, recurrent, complex or bloody cysts require mammography and biopsy, although in selected patients the so-called triple diagnostic techniques (palpation, mammography, aspiration) can be used to avoid biopsy.



Picture 4. Mammogram - Side view

Picture 5. Mammogram - Side view

Routine mammography reduces breast cancer mortality by 25 to 35% in asymptomatic women older than 50 years and probably by a smaller percentage in asymptomatic women younger than 50 years. In screening studies, about 40% of the cancers were detected by mammography but not by physical examination. Mammography for women older than 50 years should be performed yearly. However, there is considerable disagreement about screening in women 40 to 50 years. However, there is considerable disagreement about screening in women 40 to 50 years. Recommendations for this age group include annual mammography (The American Cancer Society), mammography every 1 to 2 yr (The National Cancer Institute), and no periodic mammography (The American College of Physicians, which considers the benefits of mammography for this age group to be uncertain).

Signs of early breast cancer detected by mammography include microcalcifications, subtle distortions of breast architecture, and crablike lesions that cannot be palpated. However, these abnormalities are not always found in patients who present with a mass or other suggestive signs, and the incidence of false-negative results may exceed 15%, depending partly on the techniques used and the experience of the mammographer. Suspicious areas on a mammogram that cannot be detected during physical examination may be localized by inserting two needles or wires using radiologic guidance, so that a biopsy of the lesion can be performed. The specimen should be x-rayed, and the x-ray compared with the prebiopsy mammogram to ensure that the suspicious area has been removed. Mammography is repeated when the breast is no longer tender, usually 6 to 12 wk after the biopsy, to confirm removal of the suspicious area.

Screening mammography should not be confused with diagnostic mammography, which is performed after a palpable abnormality has been detected. Diagnostic mammography is aimed at evaluating the rest of the breast before biopsy is performed, or occasionally is part of the triple test strategy to exclude immediate biopsy.

Ultrasonography helps distinguish a breast cyst from a solid mass. A cyst usually requires no treatment if the patient is asymptomatic, although some physicians believe all cysts should be aspirated and the fluid sent for cytologic studies, whereas a mass usually requires biopsy. Ultrasonography is not used in routine screening for cancer.

Picture 6. Ultrasound examination

8. CONCLUSION

Risk reduction should be considered throughout a woman's life. Women with low-to-normal risk should consider lifestyle modifications and vigilant surveillance. Such modifications should target minimizing breast cancer risk by maintaining a healthy weight, avoiding cigarettes, limiting alcohol consumption, getting regular exercise, and avoiding non-diagnostic ionizing radiation. Although these lifestyle choices have not been proven to prevent breast cancer, they are generally associated with good health and generally believed to offer some protection against cancer.

On the other hand women at high risk for the disease may consider preventive pharmacologic therapy. In some cases, prophylactic bilateral mastectomy may be an appropriate option in others; pharmacological options may be more suitable. Women who have been successfully treated for breast cancer should consider, together with their practitioners, how best to prevent recurrence.

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