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Breast cancer prevention

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.

<place and date>   <name>

Contents

<u>Introduction (explanation of the relevance of the selected topic)</u>

Breast cancer is of increasing importance especially in developed countries where it is considered the leading cause of death in women between the ages of 20-59 (Guinee VF: 1998). The aim of this thesis is to firstly discuss the epidemiology of breast cancer and secondly to analyse risk factors and preventative measures based on those risk factors. This review also covers genetic testing, screening, and prevention in high-risk patients and addresses management of a new breast cancer diagnosis in the setting of a risk gene mutation. Also discussed is the integration of magnetic resonance imaging for breast cancer screening in BRCA carriers which has achieved a higher sensitivity of the screening, and earlier detection of breast cancer. The benefits and shortcomings of prophylactic mastectomy will also be reviewed in light of new clinical trials.

It is worth mentioning that the management of these patients must be individualized and multidisciplinary based on their risk level, age and personal preference of preventative treatment.

Epidemiology of breast cancer

Breast cancer is considered the leading cause of death for women aged 20-59 years. It is the most site –specific cancer in women (Guinee VF: 1998). Of all the newly diagnosed cancers in females it accounts for 26% of the cases and 15% of cancer related deaths in women (Jemal A, et al: 2008). It was predicted that 182,460 women in the united states would be diagnosed with invasive breast cancer in 2008 and that 40,480 would die from it (American Cancer Society: Cancer Facts and Figures 2008. Atlanta). Until the year 1987, breast cancer was the leading cause of cancer related mortality when it was surpassed by lung cancer. (Figure 1).

The estimated risk for a woman in the United States to develop breast cancer was 1 in 13 in 1973, 1 in 11 in 1980, and 1 in 8 in 2004. Age adjusted incidence of new breast cancer cases had increased steadily since the mid-1940's according to cancer registries in Conneticut and Upper new York state. Data from nine surveillance, Epidemiology, and End Results (SEER) registires shows that the incidence has been decreasing by 23% per year since the year 2000. From 1973 to 1980 the increase had been approximately 1%. From 1980 to 1987 there was an increased incidence of approximately 4% as characterised by the frequent detection of small primary cancers. The increase in incidence was seen mostly in women who were aged 55 years and older and was in parallel with percentage of older women who had mammograms taken. Meanwhile there was a decrease in incidence rates for regional metastatic disease and breast cancer mortality. The 5 year overall survival rates for breast cancer from 1960 to 1963

were 63 and 46% in white and African American women respectively. The rates for 1981 to

1983 were 78 and 64% respectively and 85% and 71% for 1987 to 1989 (respectively).

Figure 1
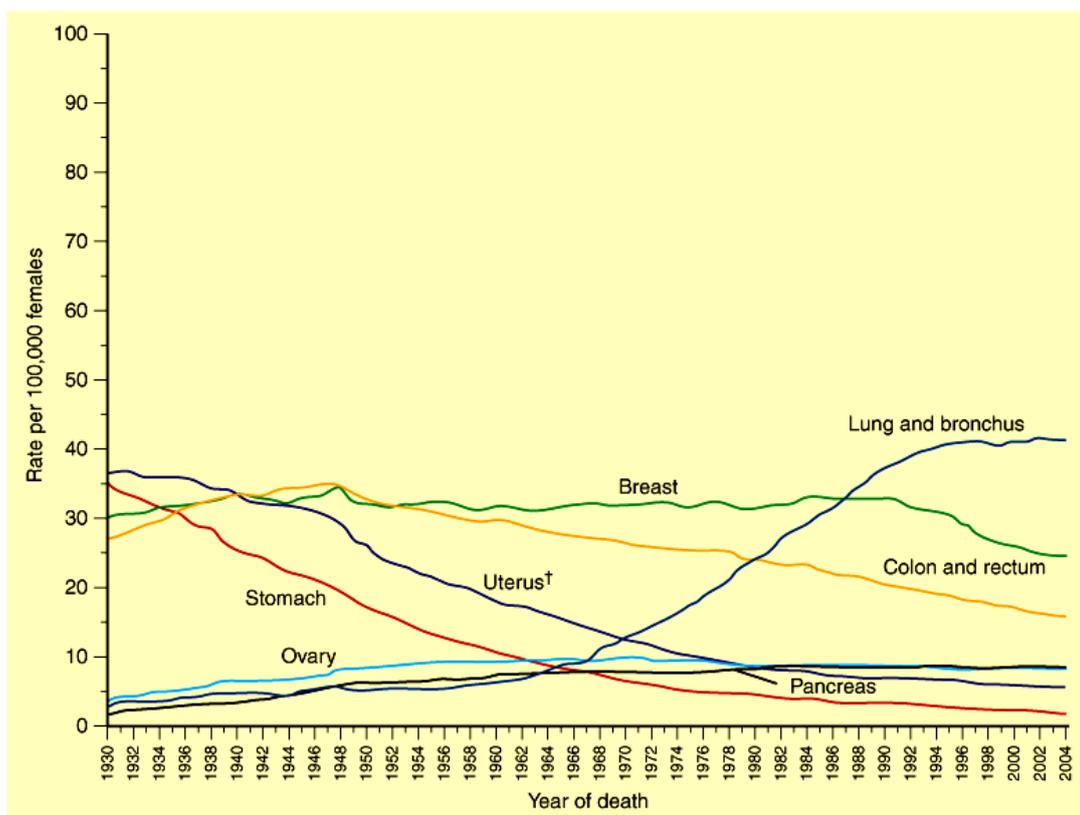
Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB,
Pollock RE: *Schwartz's Principles of Surgery, 9th Edition:* http://www.accessmedicine.com

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Death rates for cancer at selected organ sites in U.S. females. These are age-adjusted rates per 100,000 population. [†]The uterine cancer death rate is derived by combining the cervical and corpus death rates. Note the steep rise in the lung cancer death rate after 1960.

Among different countries worldwide there appears to be a 10-fold variation in breast cancer

(Figure2). The highest age adjusted mortality for breast cancer is associated with Cyprus and

Malta (29.6 per 100,000 populations). The age adjusted mortality for breast cancer in the

United States is 10 cases per 100, 000 population. Women living in industrialised countries

appear to have a higher rate of breast cancer than those in non-industrialised countries (Figure

2). However in this regards Japan seems to be an exception. Particular groups in the United States seem to have a below average incidence of breast cancer, they include Mormons, Seventh Day Adventists, American Indians, Alaska natives, Hispanic/Latina Americans, and Japanese and Filipino women living in Hawaii. Groups which seem to have above average incidence include nuns (due to nulliparity) and Ashkenazi Jewish women.

Throughout the 1990's the incidence of breast cancer increased and this trend has continued approximately 0.5% annually. The approximate prediction for 2010 was set at 1.4 million new cases. In china cancer registries have observed annual increases in incidence of up to 3 to 4% which is similar to the increases observed in eastern Asia.

One piece of good news is the fact that SEER program has shown declines in breast cancer incidence over the past decade. This decline is thought to be due to decreased usage of hormone replacement therapy attributed to Women's health initiative reports (Clarke CA, et al: 2006).

Figure2

Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB,
Pollock RE: *Schwartz's Principles of Surgery, 9th Edition:* http://www.accessmedicine.com

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International variation in breast cancer incidence and mortality.

(Reproduced with permission from Ferlay et al.[76])
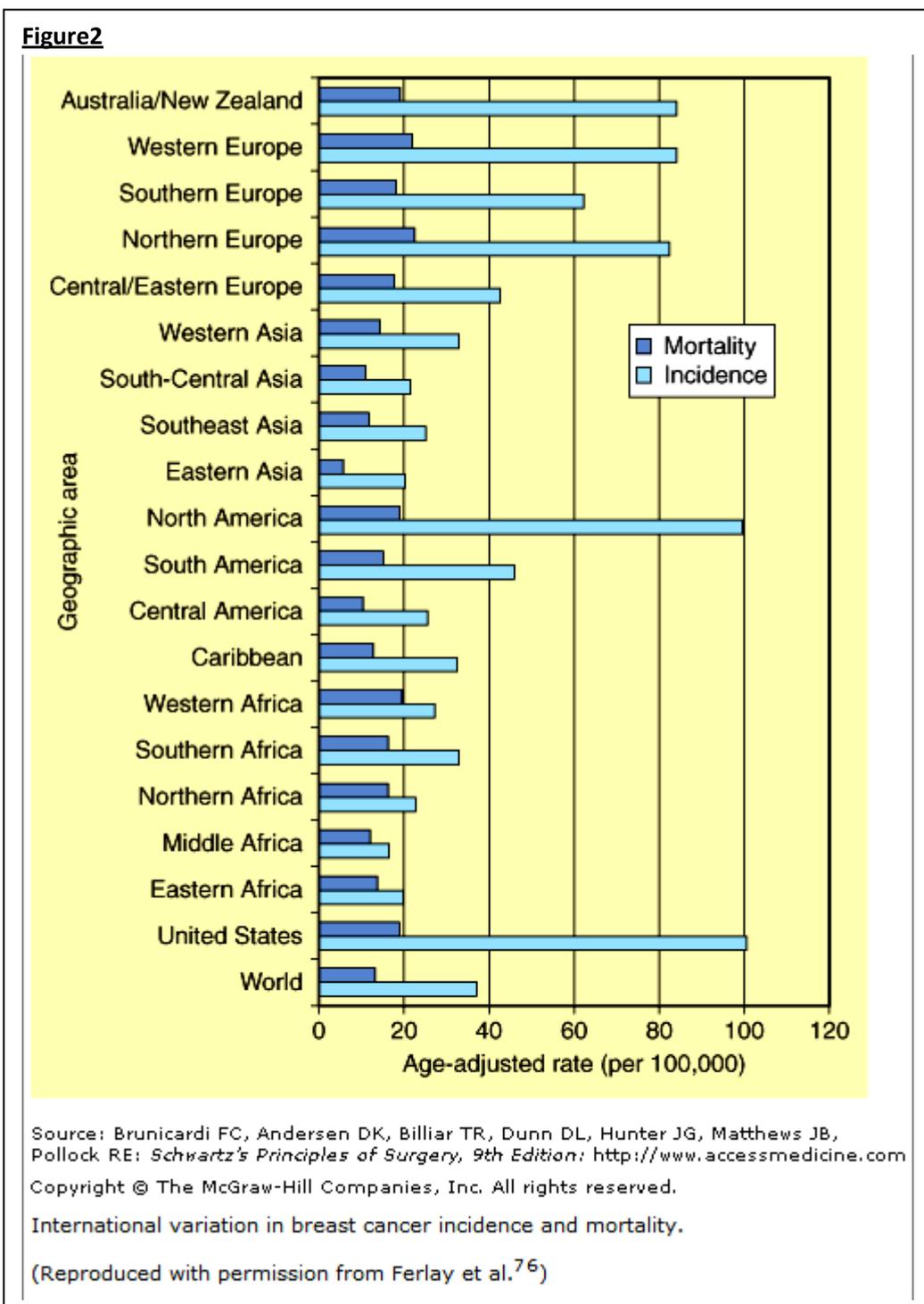
The well-defined breast cancer variables and risk factors are based on geography, regional

life style, and racial or ethnic background (Ferlay J, et al: Globocan 2002). Generally

speaking female populations of Asia and Africa, underdeveloped nations show relatively

lower breast cancer incidence and mortality rates (Figure 2.). Women from heavily

industrialised and westernised lifestyles (north American and European countries) appear to have higher breast cancer incidences and mortality rates which is especially evident in racially and ethnically diverse United States population (Ries LAG, et al: SEER Cancer Statistics Review, 1975-2002).

Figure3

Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE: *Schwartz's Principles of Surgery, 9th Edition*: http://www.accessmedicine.com
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Breast cancer incidence and mortality rates in the United States, 1998 to 2002, by ethnic background.
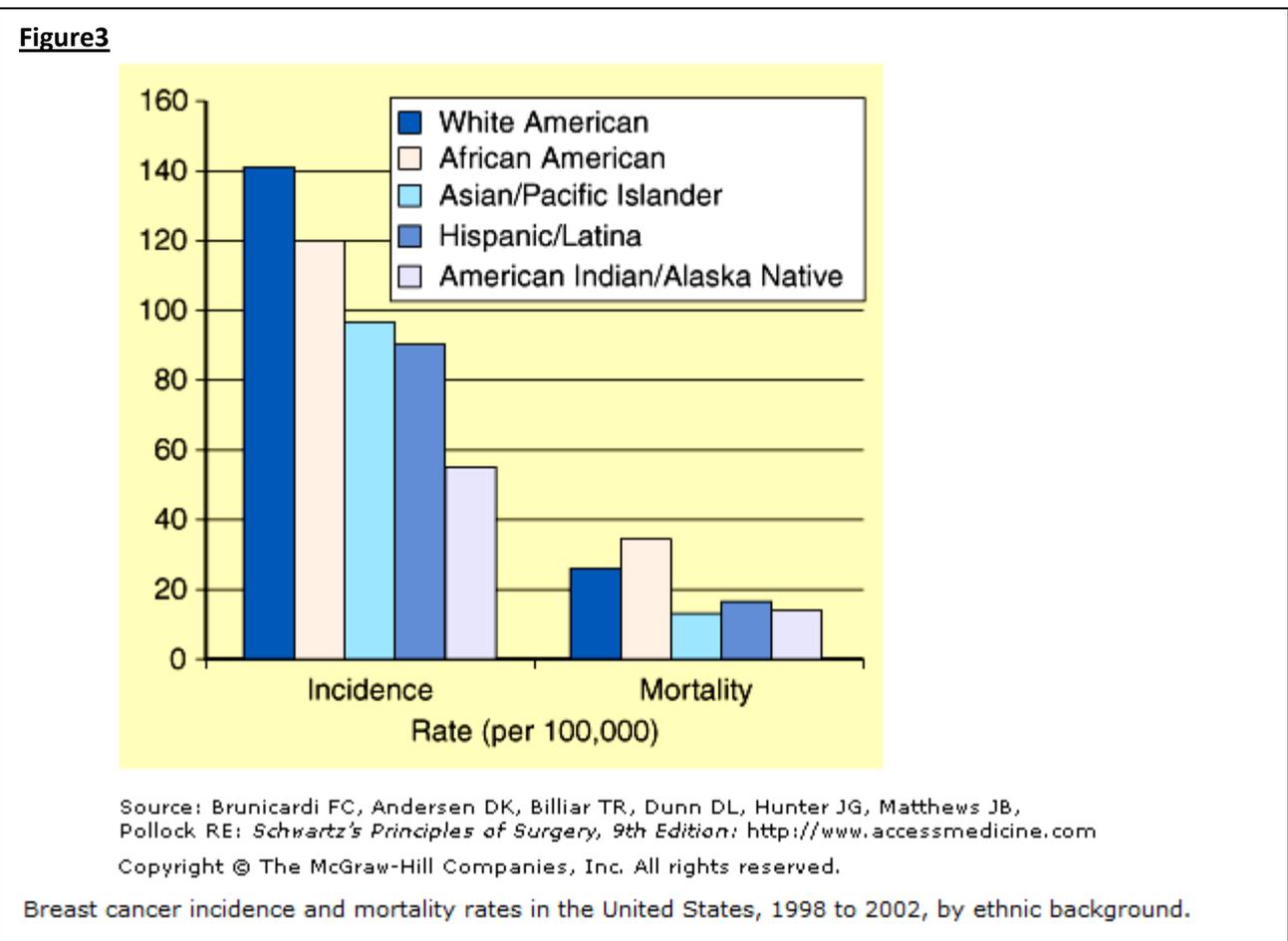
Factors influencing the incidence of breast cancer may differ from those which affect mortality although they are often related. Women who begin childbearing at young ages and who have multiple full-term pregnancies and prolonged lactation appear to have lower incidence rates. Interestingly these features usually characterise many underdeveloped nations. Underdeveloped countries however have disproportionate mortality risks which are attributed to absence of effective mammographic screening programmes for early detection

and limited access to effective cancer treatment programs. Similarly these factors are thought to be responsible for the disproportionate mortality rates between different races in the United States (Figure3.). Asian Americans (second- third generation) have a rising breast cancer incidence and mortality rates as they adopt to western lifestyles.

Minority racial and ethnic groups which include African Americans and Hispanic/latino Americans are 2-3 times more likely to lack health care insurance. The disadvantages prevent effective breast cancer screening and diagnosis, advanced stage distribution, inadequate treatment and increased mortality rates (Figure 3.). Another recent problem has been the linguistic barrier between physicians and recently immigrated and non English speaking patients which has been reported to contribute to failure of systemic therapy and breast reconstruction. Another factor in ethnic minorities is inadequately controlled co-morbidities (hypertension and diabetes) which may explain treatment disparities in this population group. There is a multifactorial cause for breast cancer disparities associated with racial or ethnic background. These disparities require a drastic improvement in public health care systems.

There are now speculations regarding hereditary factors influencing breast cancer risk in patients of certain racial or ethnic ancestry (Fregene A, Newman LA: 2005.). This can be observed in the low lifetime risk of breast cancer in African Americans as compared with White Americans and conversely higher mortality rates in African Americans (Figure 3.). The latter group also has highest incidence of breast cancer among women <45 years of age. Most importantly the incident rates for estrogen receptor-negative tumors also appear to be

highest in African American women of all ages. The same pattern can be seen in female populations in sub-Saharan and western Africa. There also appears to be an increased frequency of male breast cancer in both African American and African males.

Natural History

One of the most significant studies describing the natural history of breast cancer was carried out by Bloom and colleagues based on the records of 250 women with untreated breast cancers (Figure 4.). These women were cared for on charity wards in Middlesex Hospital, London between 1805 and 1933. After the initial diagnosis the median survival of the population was found to be 2.7 years after the initial diagnosis (Bloom HJ, Richardson WW, Harries EJ: 1962.).
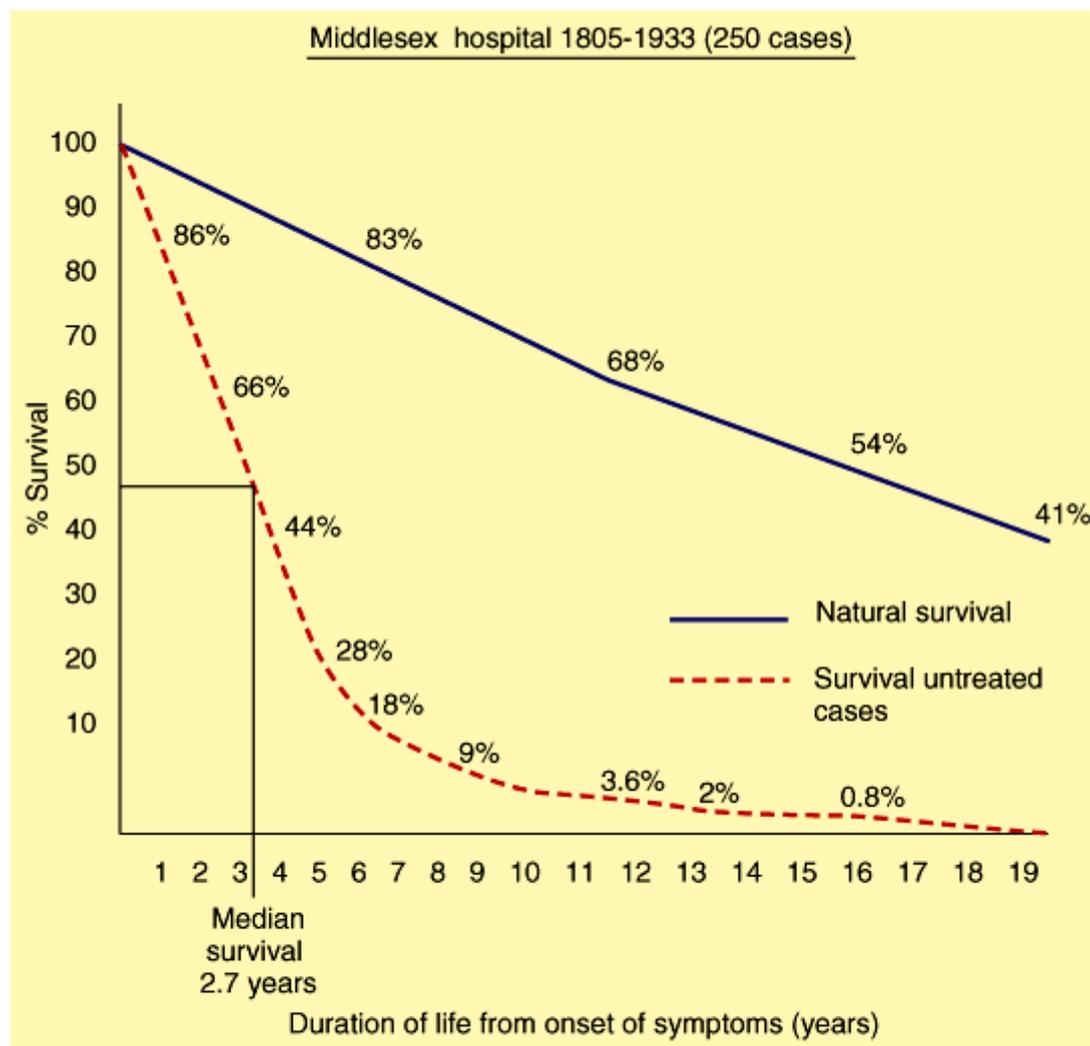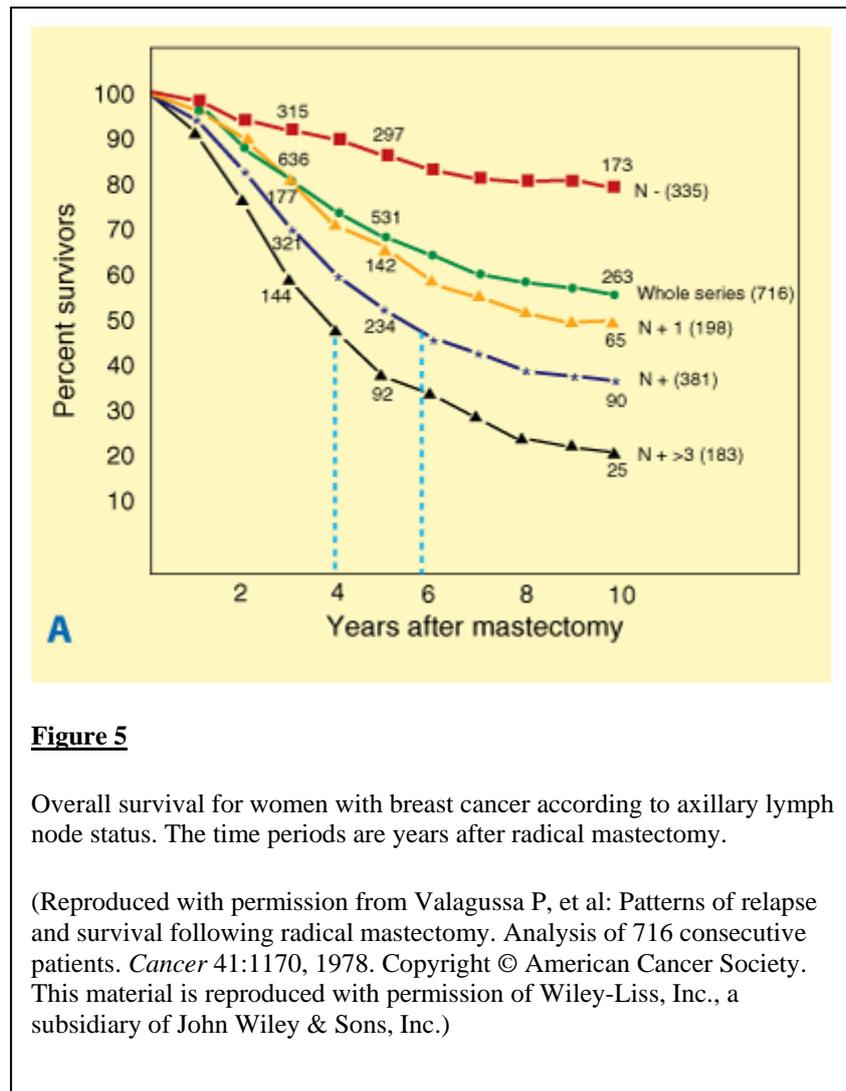
Figure4

Survival of women with untreated breast cancer compared with natural survival.

[Reproduced with permission from Bloom HJG, Richardson WW, Harries EJ: Natural history of untreated breast cancer (1803–1933): Comparison of untreated and treated cases according to histological grade of malignancy. *Br Med J* 2:213, 1962. With permission from the BMJ Publishing Group.]

The five and ten year survival rates in these women were found to be 18 and 3.6% respectively. The survival rate of 15 years or longer was found in only 0.8%. The causes of death in the women were confirmed by autopsy reports and 95% were confirmed to have died from breast cancer while 5% died of other causes. Ulceration of the breast was observed in in almost 75% of the women, during the course of the disease. The longest surviving patient was reported to have died in the 19th year after diagnosis.

Primary Breast Cancer

Primary breast cancer constitutes more than 80% of breast cancers and involves epithelial and stromal tissues which show productive fibrosis. Morphologic changes in breast tissues are observed such as characteristic skin retraction. Peau d'orange (otherwise known as localised edema) is another change which develops due to disruption of lymph fluid from skin. Continual growth and cancer cell invasion of the skin leads to ulceration with small satellite nodules surrounding it. There is a direct correlation between the size of the primary breast cancer and disease free period and overall survival. A particularly close relation is observed between cancer size and axillary lymph node involvement (Figure 5.)

Figure 5

Overall survival for women with breast cancer according to axillary lymph node status. The time periods are years after radical mastectomy.

(Reproduced with permission from Valagussa P, et al: Patterns of relapse and survival following radical mastectomy. Analysis of 716 consecutive patients. *Cancer* 41:1170, 1978. Copyright © American Cancer Society. This material is reproduced with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

Generally breast cancer recurrences are mostly distant (>60%), while 20% are local-regional, and the remaining 20% are both local-regional and distant.

Axillary Lymph node Metastasis

The transport of cancer cells via lymphatic network of the breast to regional lymph nodes (especially axillary lymph nodes) occurs as the size of the primary cancer increases. The consistency of these lymph nodes while ill defined and soft at first become firm and hard with continued growth of the metastatic cancer. Eventually a conglomerate mass is seen as a result of lymph nodes adhering to one another.

B. Risk of metastases according to breast cancer volume and diameter.

Figure 6. (Reproduced with permission from Koscielny S et al: Breast cancer: Relationship between the size of the primary tumour and the probability of metastatic dissemination. *Br J Cancer* 49:709, 1984.)
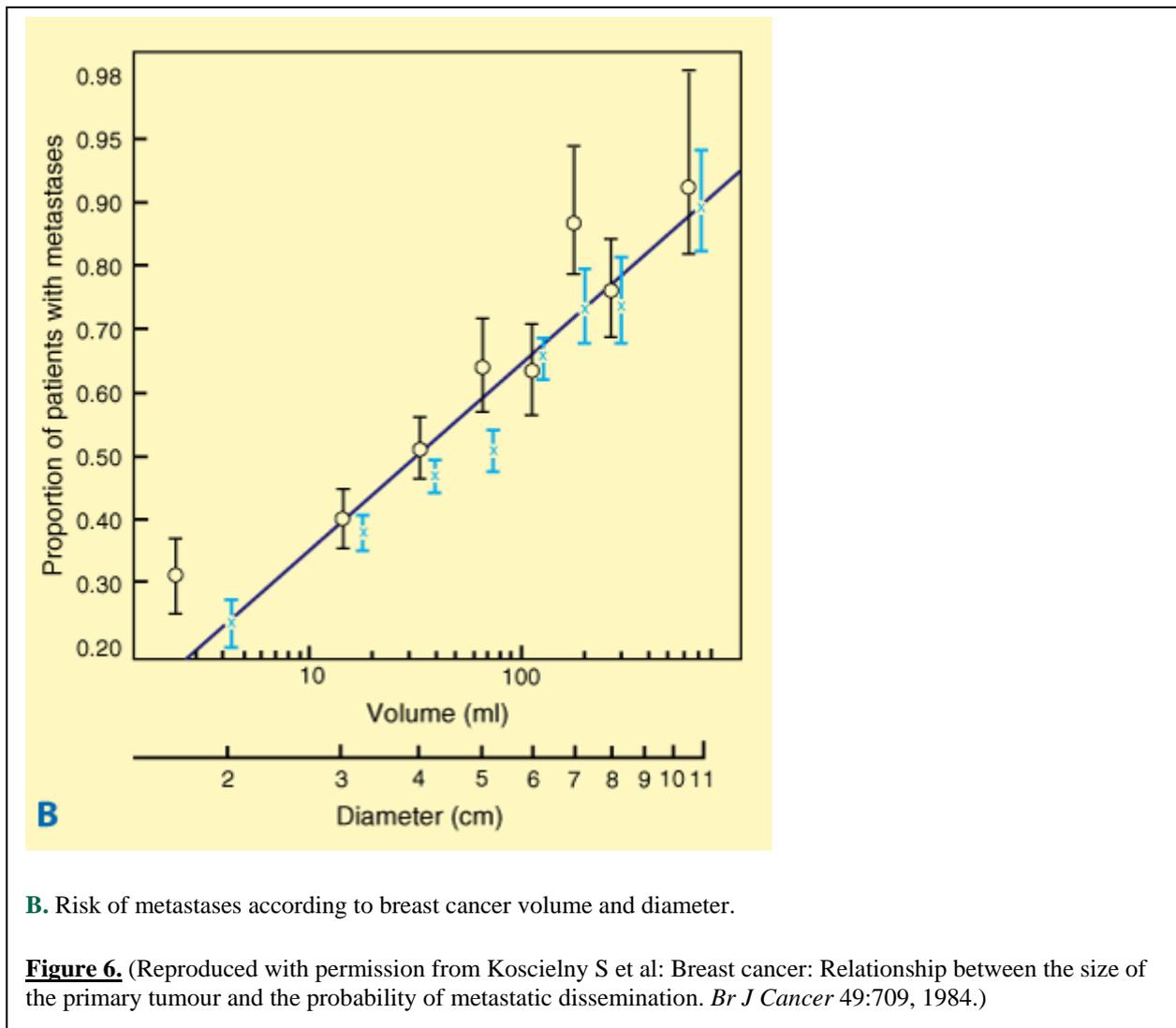
The growth cancer cells through node capsule and their fixation to contiguous structures in axilla such as the chest wall is a common occurrence. These axillary lymph nodes are divided sequentially from low (level I), to the central (level II) to the apical (level III) lymph node groups. The most important prognostic correlate of disease free and overall survival is axillary lymph node status. Despite this more than 95% of deaths in women with breast cancer are due to distant metastasis (Figure 6). Those women who suffer from the node

negative form of the disease have <30% risk of recurrence. The recurrence is noted to be as high as 75% for women with node positive disease.

Distant Metastasis

Neovascularization is a process whereby breast cancers acquire their own blood supply. This occurs at approximately the 12th cell doubling. From here onwards cancer cells may be shed directly into systemic venous blood and seed pulmonary circulation via either the axillary and intercostals veins or the vertebral column (Batson's Plexus of veins). Natural killer lymphocytes and macrophages scavange the cancer cells. After the primary cancer becomes larger than 0.5 cm in diameter implantation of metastatic foci from breast cancer occurs. This process usually corresponds with the 7th cell doubling. Distant metastases have been shown to be the main cause of death in breast cancer patients for upto 10 years after initial treatment. This means that conclusive results from breast cancer trials can only be derived until at least 5 to 10 years have elapsed. In women who do develop distant metastasis 60% usually do so within 24 months of treatment, unfortunately this metastasis only becomes evident only 20-30 years after treatment of the primary cancer. Common sites of distant metastasis for breast cancer include bone, lung, pleura, soft tissues and Liver.

Risk factors for breast cancer

Factors are broadly divided into those useful in clinical practice (which significantly influence odds of contracting breast cancer in individual woman), and those important in large public health trends in populations. The risk factors are summarised in Figure 7. The incidence of breast cancer in males is less than 1% of the incidence in females.

Figure7.

| Risk Factors for Breast Cancer |

Factors Important in Populations

    Age at menarche and menopause

    Parity

    Age at first birth

    Breast-feeding

    Exogenous hormone use or exposure

    Alcohol consumption

Factors Important in Individual Patients

    Gender (female >> male)

    Age (steady increase with age)

    Family history (mothers, sisters, daughters)

    History of previous breast cancer (noninvasive or invasive, ipsilateral or contralateral)

Histologic Risk Factors

    Proliferative breast disease

    Atypical ductal hyperplasia (ADH)

    Atypical lobular hyperplasia (ALH)

    Lobular carcinoma in situ (LCIS)

Age and Gender

Age and gender is, considered as probably the most important risk factor particularly in everyday clinical practice. With advancing age the incidence of breast cancer increases in the female population. Conversely breast cancer is considered rare in persons younger than 20 years. Cases in women younger than 30 are reported to be less than 2% of total cases. By age 40 the incidence rises to 1 in 93, and 1 in 50 by age 50, eventually rising to 1 in 10 by age 80 (300 cases per 100 000).

Family History and Genetic Risk Factors

The relation between family history and the risk of breast cancer has been examined closely over the years in many studies which can be summarised as follows:

1.   First-degree relatives (mothers, sisters, and daughters) of patients with breast cancer have a twofold to threefold excess risk for the disease.

2.   Risk decreases quickly in women with distant relatives affected with breast cancer (cousins, aunts, grandmothers).

3.   Risk is much higher if affected first-degree relatives had premenopausal onset and bilateral breast cancer.

The absolute risk in first degree relatives approaches 50%, especially in those with bilateral and early onset cancer. This is consistent with Autosomal dominant mode of inheritance (Domchek S, Weber BL 2004).

Genetic factors

Genetic factors are believed to cause 5-10% of all breast cancer cases, 25% of whom younger than 30 years. The long arm of chromosome 17 (17q21) was identified as the cancer susceptibility gene, in a study in 1990 (led by Marie-Claire King). In 1994 the gene BRCA1 was discovered and thought to account for 40% of familial breast cancer. BRCA2 gene was discovered one year later, thought to be the second susceptibility gene. Women with mutations in either gene are also at increased risk of ovarian cancer, though to be 45% lifetime risk for BRCA1 carriers.

Deleterious mutations in general population have a frequency of about 1 in 1000.

The chance of carriers of mutations (of BRCA1 & 2) developing breast cancer (otherwise known as penetrance) is placed at 56%. The lifelong rates of breast cancer are between 50-70% for carriers.

BRCA mutations

Mutations in BRCA1 and BRCA2 are inherited in an autosomal dominant manner and are responsible for 5-10% of breast cancers (Ford D, et al: 1998. Wooster R, Weber BL: 2003.). Both BRCA 1 and BRCA2 function as tumour suppressor genes, the loss of both alleles for each gene is required for initiation of cancer.

BRCA1

The isolation of BRCA1 gene has suggested roles transcription, cell cycle control, and DNA damage repair pathways. As mentioned before, BRCA1 gene is inherited in a autosomal dominant fashion and the gene is located on chromosome 17q. Its size is roughly 100 kilobases (kb) of DNA containing 22 coding exons. The full length messenger RNA is 7.8 kb and encodes 1863 amino acids. Sequence variations in BRCA1 are thought to be more than 500.

Inactivation of a single inherited allele by germaline mutation is followed by elimination of remaining allele causing cancer. The gene product can have a variety of effects among them

negative regulation of cell growth or recognition and repair of genetic damage and even spontaneous mutation are all possible.

BRCA1 mutations lead to tumours that are both high grade and hormone receptor negative and aneuploid with increase S-phase fraction. Basal like tumours are closely associated with BRCA1 mutations, 10% of which are found to carry the mutation. Invasive ductal carcinomas are in general associated with BRCA1, they are poorly differentiated and hormone receptor negative. BRCA1-associated cancer histopathology is worse compared with BRCA2-asscoaited cancer

The distinguishing clinical features of BRCA1 include early age of onset (as compared with sporadic cases), higher prevalence of bilateral breast cancer, presence of associated cancers in some affected individuals (especially ovarian and possibly colon and prostate cancers).

In as many as 45% of hereditary breast cancers and 80% of hereditary ovarian cancers, germline mutations in BRCA1 are represented. Lifetime risk for developing breast cancer and ovarian cancer are vastly increased in female mutation carriers (90% and 40% respectively). Of the children of carriers approximately 50% inherit the trait.

Founder mutations (preferential mutations in closed populations) include 185delAG and 5382insC mutations in BRCA1, found in Ashkenazi Jewish population. The mutations are at 10 fold higher frequency in Ashkenazi Jews than non-white jewish population. The carrier frequency of 185delAG in jewish population is 1% and along with 5382insC accounts for all

BRCA1 mutations in this population. By analysing the germline mutations in Jewish and non-jewish women with early onset breast cancer it was found that 20% of women who develop breast cancer before age 40 years carry 185del AG mutation.In French Canadian families, BRCA1, C4446T mutation is most common.

BRCA2

The location of BRCA2 gene is on chromosome arm 13q and has a size of approximately 70kb of DNA. Twenty six coding exons are present in the 11.2 coding region (Ford D, et al: 1998.; Wooster R, Weber BL: 2003). It encodes a protein of 3418 amino acids.

BRCA2 has no homology to any previously described gene, and the protein contains no previously defined functional domains. Its biologic function is not well defined but not unlike BRCA1. The susceptibility of breast cancer in BRCA2 families is an autosomal dominant trait with a high penetrance. An estimated 50% of children of carriers inherit the trait. It accounts for 30% of familial breast cancer. It is thought to play a role in DNA damage response pathways. BRCA2 messenger RNA has also been proven to be present in late G1 and S phases of cell cycle. In terms of kinetics in the cell cycle, BRCA2 is similar to BRCA1 protein. This suggests the possibility of these genes being co-regulated.

The mutational spectrum of BRCA2 is not as well established as BRCA1 and until now more than 250 mutations have been found. BRCA2 mutation carriers have a breast cancer risk of roughly 85%, and life time ovarian cancer risk close to 20%.

BRCA2, is associated with increased breast cancer risk in males. Men with germaline mutations in BRCA2 have an estimated breast cancer risk of 6% which represents a 100 fold

increase over the risk in the general male population. Mutations in BRCA2 in women have a lifelong risk (20-30%) for ovarian cancer.

Founder mutations of BRCA2 affect Askenazi jews (617delT mutation present in 1.4%) and French Canadians (8765delAG mutation), and the Icelandic population (999del15 mutation). Of the general population of Iceland, 0.6% carry the stated mutation.

Distingiushing clinical features of BRCA2 associated breast cancer include early onset age (compared with sporadic cases), higher prevalence of bilateral breast cancer, and presence of associated cancers in some affected individuals (Ovarian, colon, prostate, pancreatic, gall bladder, bile duct, stomach cancers, Melanoma). Cancers associated with BRCA2 mutations are invasive ductal carcinomas, which are typically hormone receptor positive. These are more likely to express hormone receptors than BRCA1-associated cancers, and are more likely to be well differentiated.

Mortality rates in those with sporadic breast cancer are similar to those with BRCA1 or BRCA2 associated cancer. It is worth bearing in mind the need for increased screening versus chemoprevention in individuals with mutations, as well as benefits of prophylactic mastectomy

Identification of BRCA mutation carriers

Genetic testing is a difficult procedure due to the large BRCA1 gene (22 coding exons) and mutations (more than 500), which are unique and limited to a given family.

The hereditary risk for breast cancer is calculated in a four step process which includes 1) obtaining a complete, multigenerational family history, 2) assessing the appropriateness of genetic testing for a particular patient, 3)Patient counselling and 4) interpretation of the testing results (Warner E, et al: 1999.). It is worth noting that genetic testing must always be in conjuction with patient education and counselling, including referral to a genetic counselor. Initially the aim is to determine whether or not the individual is a candidate for genetic testing and whether genetic testing would be of any use for both personal and clinical decision making. This process requires a complete and thorough family history, where both maternal and paternal sides of the family are assessed. The paternal inheritance is important as 50% of the women with BRCA mutation have inherited the mutation from their fathers.

Statistically based models determining the likelihood of individuals carrying a BRCA mutation, have been developed to aid surgeons advice women about testing. Indications for considering hereditary breast cancer as a risk are considered if a family has 2 or more women who developed ovarian cancer or breast cancer before the age of 50 years. Meanwhile women diagnosed with breast cancer before age 50 years or ovarian cancer at any age, are asked about first, second, and third degree relatives, on either side of the family with either of these

diagnoses. Other high risk groups include breast and ovarian cancer in the same individual, and male breast cancer at any age. Individuals from high risk ethnic groups have a higher possibility of hereditary cancer. For example Ashkenazi Jewish women are always considered for early onset breast cancer.

BRCA mutation testing

As mentioned before appropriate counselling for individuals being tested for BRCA mutation is strongly recommended along with documentation of informed consent (Warner E, et al: 1999; Schneider KA 1997.). Gene sequence analysis is a clinical test available for analysing BRCA mutation gene. A different and more effective strategy is recommended for a family with a history suggestive of hereditary breast cancer and no previously tested member. The strategy for the latter is to first begin testing an affected family member who will undergo complete sequence analysis for both BRCA1 and BRCA2 genes. In case a mutation is identified the relatives are then tested only for that specific mutation. If the individual is of Ashkenazi Jewish Ancestry, they are tested initially for 3 specific mutations most likely in their population which account for hereditary breast and ovarian cancer. If the initial testing is negative there may then be a need for a full analysis of the BRCA1 and BRCA2 genes.

A positive test result is defined as the presence of BRCA mutation that interferes with translation or function of the BRCA protein. Women with deleterious mutations have 85% breast cancer risk along with a greatly increased risk of ovarian cancer. Negative test results

are based on the individual's personal and family history especially whether a mutation has been previously identified in the family which would require testing only for that specific mutation. If the mutation is absent the women has no greater risk of developing cancer than that of the general population. Additionally, no BRCA mutation can be passed on to woman's children.

A negative test result in an affected individual, in the absence of a previously identified mutation shows that BRCA is not possible for familial cancer. But the possibility of an unusual abnormality in one of these genes which cannot yet be identified through clinical testing remains. Another possibility is a situation known as Phenocopy, where the familial cancer is caused by an identifiable BRCA mutation but the individual tested had sporadic cancer. This is seen especially in individuals developing breast cancer close to the age of onset of the general population (60 years or older). The false negative rate for BRCA mutation testing is <5%. Single base pair change (missense mutation) are characteristically difficult to interpret as they donot always result in a non functional protein. This means that they are sometimes reported as indeterminate results especially if not located within functional domains or those causing minimal protein structure changes. Hence it is always important to emphasize that further research may clarify indeterminate results. Some clarification may be gained by testing other family members with breast cancer and to determine any genetic variant tracks. Currently 12% of test results are classified as indeterminate genetic variance.

In countries without universal health care plans, concerns have been raised that identification of hereditary risk for breast cancer may interfere with obtaining affordable health insurance. The concern stems from discrimination that may be directed at an individual or family based

on an apparent or perceived genetic variation from thr normal human genotype. In the United States it was made illegal for group health plans to consider genetic information as pre-existing condition or to use it to deny or limit coverage. The health insurance portability and accountability Act (HIPAA) was passed in 1996 it meant that individuals applying for health insurance are not required to report whether relatives have undertaken genetic testing for cancer risk, only when relatives have actually been diagnosed with cancer. At present there appears to be little documented evidence of genetic discrimination as a result of available genetic tests.

Lobular Carcinoma In Situ and Personal History

Breast biopsy diagnosis if found to be abnormal represents an important risk factor category. Equally history of mammary cancer in one breast increases the probability of a consequent primary tumour in the other breast. The RR (ratio of observed cases over expected cases) in contralateral breast cancer is shown to be between 3 and 4 after breast cancer in one breast (Rosen PR: Rosen's Breast Pathology, 2001; . Lyman GH, et al: 2005). The age diagnosis of the first primary cancer affects the magnitude of RR. The risk for the cancer in the remaining breast is 5-6 times higher(than the general population) in patients younger than 45. The risk decreases to a twice or less increased risk if the patients are older than 45 years. In other words the risk factor of 1% per year in young patients translates to 0.2% in older patients. ((Rosen PR: Rosen's Breast Pathology, 2001; Lyman GH, et al: 2005).

Lobar Carcinoma In situ (LCIS) is usually an incidental biopsy finding usually for another condition. LCIS does not manifest as calcifications in mammography, nor does it form a palpable mass. It is relatively uncommon condition seen mostly in younger pre-menopausal women. The largest collected series of patients with LCIS were studied in a review by Haagensen. The study showed LCIS was diagnosed in 3.6% of the patients, who were biopsied for benign disease. The study determined that the likelihood of carcinoma developing in by 35 years of age was 21.4%. These findings, when compared with the Connecticut tumour registry data, give a risk ratio of 7:1 (observed to expected cases). It was shown that 40% of the subsequent carcinomas were purely in situ lesions, of the ductal type and not lobar. Of these half occurred in the contralateral breast. This shows that LCIS is acting as a histologic marker for increased breast cancer susceptibility, estimated to be slightly less than 1% per year.

The usual approach to patients with LCIS is conservative rather than mastectomy. Standard care relies on close observation with or without tamoxifen chemoprevention. Patients must be informed of the risk of LCIS and its predisposition to subsequent carcinoma along with lifelong risk which increases with age. It is thought that biopsy of opposite breasts adds little useful information because the risk of subsequent breast cancer is equal for both breasts. Treatment with tamoxifen (5 year course) can provide a 56% reduction in breast cancer risk. Bilateral total mastectomy remains the procedure of choice for patients who prefer surgery to observation. It is worth noting that subcutaneous mastectomy is not an appropriate method of cancer prevention because it retains breast glandular cells in the nipple and behind areola.

Other Histologic Risk Factors

An important risk factor for the eventual development of breast cancer is Benign breast disease. Histologic changes and lesions show either proliferative or non-proliferative alterations. Non-proliferative changes don't cause significant increase in female lifetime risk for breast cancer. The histological changes seen in non-proliferative changes include mild to moderate hyperplasia of luminal cells within breast ducts. Proliferative changes on the other hand show excess risk for breast cancer. Proliferative lesions can be further subdivided according to **Dupont and Page**, into those with atypical epithelial hyperplasia and those without atypia (otherwise known as severe hyperplasia). In summary, the lesions include: nonproliferative lesions, proliferation of breast epithelium without atypia (severe hyperplasia), and proliferation with atypia (includes ADH and atypical lobular hyperplasia (ALH)). Women with either ADH or ALH have an RR which is between 4 and 5 times higher than control population of women. This risk increases to nine times in those with positive family history and atypical hyperplasia. Hence the annual risk for development of breast cancer in women with LCIS is slightly less than 1% per year which increases to 0.5% and 1% per year with ADH, or ALH. Factors which influence these figures include age at diagnosis, menopausal status, and family history. (overview in Figure 8.)

Figure 8.

Table 34-3 -- Histologic Risk Factors for Breast Cancer [*]

HISTOLOGIC DIAGNOSIS	RELATIVE RISK ESTIMATES [†]
Nonproliferative disease [‡]	1.0
Proliferative disease without atypia [§]	1.3-1.9
Proliferative disease with atypia [¶] and a strong family history and premenopausal or age ≥50	3.7-4.2
	4-9
	5-7
Lobular carcinoma in situ (LCIS)	>7

* Estimates have been compiled from several sources, including (1) Hartmann LC, Sellers TA, Frost MH, et al: Benign breast disease and the risk of breast cancer. N Engl J Med 353:229, 2005; (2 Connolly JL, Schnitt SJ, Colditz GA: A prospective study of benign breast disease and the risk of breast cancer. JAMA 267:1780, 1992; (3) Dupont WD, Parl FF, Hartmann WH, et al: Breast can associated with proliferative breast disease and atypical hyperplasia. Cancer 71:1258, 1993.

† Ratio of observed incidence over the incidence in women without proliferative disease.

‡ Fibrocystic change with no, usual, or mild hyperplasia.

Reproductive risk factors

Increased risk for the developing breast cancer is associated with increased exposure to estrogen. Conversely reducing the exposure is thought to be protective (Bernstein L, et al: 1994. Wynder EL, et al: 1997.). Estrogen exposure is increased during early menarche, nulliparity and late menopause. Several milestone periods exist and include, menarche before 12 years of age, first live childbirth after age 30, nulliparity and menopause after age 55. Conversely each 2 year delay in menarche is associated with a 10% reduction in breast cancer. This risk doubles with menopause after age 55. Consequently any factors that increase number of menstrual cycles are associated with increased risk. Protective factors, in this context are those which decrease the total number of menstrual cycles such as moderate levels of exercise and longer lactation period.

Full term pregnancy is associated with terminal differentiation of breast epithelium and is protective. Conversely older age at first birth is associated with increased risk of breast cancer. The risk of developing breast cancer is halved in women who have full term first pregnancy before age 18, compared with those after age 30. Induced abortion has shown neither a positive nor a negative effect on breast cancer risk.

Generally speaking reproductive factors appear to be relatively mild (RR from 0.5-2.0) compared with gender, age, histologic risk factors, and genetics. But unlike family history and histologic factors, reproductive risk factors affect everyone and tend to have a large influence on the prevalence of breast cancer in populations. (Hartmann LC, Sellers TA, Frost MH, et al: 2005)

Obesity is also associated with increased risk of breast cancer due to the role of adipose tissue as the site of conversion of androstenedione to estrone, thereby providing a major source of estrogen in postmenopausal women and increasing the exposure.

Exogenous Hormone Use

Exogenous hormones are most commonly used as oral contraceptives in premenopausal women and post menopausal hormone replacement therapy, menstrual irregularities, polycyctic ovaries, fertility treatment, hormone insufficiency states. In users of oral contraceptives no apparent increased risk has been detected. The RR is close to 1.0 (for both current and past users) (Hartmann LC, Sellers TA, Frost MH, et al: 2005; Fisher B, Dignam J, Wolmark N, et al: 1998).

A randomised controlled trial of healthy post menopausal women 50-79 years of age was conducted by Women's health initiative. The benefits and risks associated with hormone replacement therapy, low fat diet, vitamin D and calcium supplementation were assessed. The study focused on rates and incidence of cancer, cardiovascular disease and osteoporosis related fractures. The individuals received various dietary and vitamin supplements and postmenopausal hormone replacement therapy. The subjects were a total of 16,608 women and were randomised to receive combined conjugated equine estrogens (e.g. Premarin, 0.625 mg/day) plus medroxyprogesterone acetate (2.5 mg/day) or placebo. The duration of the study was from 1993-1998 at 40 centres in United States. Baseline and yearly mammography and clinical breast examinations were performed. A stopping rule of 5.2 years of follow-up was set. The cases of reported breast cancer stood at 245 cases (invasive and non-invasive) in the combined hormone replacement group compared with 185 cases in the placebo group (RR= 124; P <0.001). Tumors in women taking combined hormone replacement therapy were suggested to be larger and more likely to be node positive. The second part of the study (reported in 2006) included women who had hysterectomy and were randomised to estrogen only versus placebo.

Total of 10,739 women with estrogen only supplementation, after 7 years of follow up had equivalent rates of breast cancer (RR= 0.88; 95% CL, 0.62-1.04) between control and treatment groups. The only statistically significant difference between the groups was higher short-interval mammographic follow-up examinations in hormone group (36.2% versus 28.1%) over the life of the trial. In conclusion there is an approximate 20% increased risk for

breast cancer in women receiving combination hormone replacement therapy with both estrogen and progesterone for 5 years.

Other Non-hormonal risk factors

These factors include radiation exposure, especially in women who receive mantle radiation therapy for Hodgkin's lymphoma. The mentioned individuals have a breast cancer risk 75 times greater than age matched control subjects. A good historical example is also the survivors of the atomic bomb blasts in Japan during World war II which had a very high incidence of breast cancer due to somatic mutations induced by radiation exposure. In these situations the deleterious effect is magnified during adolescence which is a period of active breast development.

Alcohol consumption is also shown to be a risk factor, increasing the incidence of breast cancer with increased consumption. Increased alcohol intake has shown to increase serum levels of estrodiol. Long-term consumption of high fat content food also increases serum estrogen levels thereby increasing risk of breast cancer.

Risk Assessment Tools

Risk assessment Models

The estimated lifetime risk of breast cancer for newborns in U.S is 12% (Claus EB, Risch N, Thompson WD: 1994; Domchek SM, et al: 2003.). With increasing age, a cancer free women, has a lower risk of developing breast cancer. Hence a 50 year old woman has an 11% lifetime risk of developing breast cancer and consequently a 70 year old has a 7% lifetime risk. Evaluating risks posed by combination of risk factors is difficult because risk factors of breast cancer are known to interact.

Currently 2 risk assessment models are used to predict the risk of breast cancer. The breast cancer Detection Demonstration Project (by Gail and Co workers), was used in the development of a model for breast cancer risk. The Gail model is the most frequently used and was developed from a mammography screening program conducted in the 1970's. This model takes into consideration age, race, age at menarche, age at first live birth, number of previous breast biopsies, presence of proliferative disease with atypia, and number of first-degree female relatives with breast cancer. The cumulative risk of breast cancer is then predicted according to decade of life. The model does not however include detailed genetic information hence may underestimate the risk for BRCA1 or BRCA2 mutation carrier and underestimate it in non-carriers. The model (known as the Gail model for breast cancer risk),

was used in the design of Breast cancer prevention trial. The mentioned trial randomly assigned women at high risk to receive tamoxifen or a placebo.

The actual calculation involves translating a woman's risk factors into an overall risk score. This is achieved by multiplying her relative risks from several categories. The risk score is then compared to an adjusted population risk of breast cancer to determine the individual risk of breast cancer in the woman. A software programme has been designed to incorporate the Gail model and is available from the National Cancer Institute at http://bcra.nci.nih.gov/brc. Recently the model has been modified to more accurately assess the risk in African American women (Gail MH, et al: 2007; Edwards BK, et al: 2005)

The Other frequently used model is based on assumptions about the prevalence of high penetrance breast cancer susceptibility genes (Claus EB, et al: 1993.). This model is referred to as the Claus model and was developed by Claus and colleagues using data from the Cancer and Steroid Hormone Study (Claus EB, et al: 1993.). The Claus model incorporates more information about family history but excludes other risk factors. This model hence provides individual estimates of breast cancer risk according to decade of life, based on the presence of first- and second-degree relatives with breast cancer and their age at diagnosis.

It is worth noting that certain risk factors are not included in either Gail or Claus risk assessment model, commonly risk factors which are less consistently associated with breast cancer (diet, use of oral contraceptives, lactation) or those rare in general population

(radiation exposure). Other proposed models account for mammographic breast density (Chen J, et al: 2006. Kerlikowske K, et al: 2007), none of which takes into account risk associated with BRCA1 and BRCA2 mutations.

MANAGEMENT OF HIGH-RISK PATIENTS /Risk management

The clinicians aim here is to consider and prioritize risk factors and make recommendations about screening and intervention. In women who may have individual risk factors for breast cancer the options include close surveillance with clinical breast examination, mammography, and possibly breast MRI. Interventions include chemoprevention with tamoxifen or raloxifen or bilateral mastectomy.

A Woman's underlying risk of developing breast cancer may affect several key decisions (Fisher B, et al: 1998.; Wu K, Brown P: 2003.). Such as the use of postmenopausal hormone replacement therapy, age of first mammography screening, when to use tamoxifen or prolphylactic mastectomy as prevention of breast cancer. Postmenopausal hormone replacement therapy, because of its effectiveness in controlling the symptoms of estrogen deficiency (hot flushes, night sweats, sleep deprivation, osteoporosis and cognitive changes) as well as reduction of coronary artery disease, was widely prescribed in the 1980's and 1990's. Unopposed estrogen increased the risk of uterine cancer and therefore the combined use of estrogen and progesterone became standard in women who had not undergone hysterectomy. Large scale phase III clinical trials were implemented to evaluate the risk vs.

Benefits of postmenopausal hormone replacement therapy. Studies were carried out by the national institute of health as a series of clinical trials to study the effects of diet, nutritional supplements and hormones on the risk of cancer, cardiovascular disease and bone health in post-menopausal women. The initial findings released in 2002, demonstrated conclusively a 3-4 fold breast cancer risk after > 4 years of use. There was no significant reduction in either coronary artery or cerebrovascular risks.

Cancer Prevention for BRCA Mutation carriers

Risk management strategies for BRCA1 and BRCA2 include:

1. Prophylactic mastectomy and reconstruction

2. Prophylactic oophorectomy and hormone replacement therapy

3. Intensive surveillance for breast and ovarian cancer

4. Chemoprevention

While Mastectomy reduces the likelihood that BRCA1 and BRCA2 mutation carriers developing breast cancer, women continue to be at risk because the germline mutation continues to be present in any remaining breast tissue. Postmenopausal women who are BRCA1 and BRCA2 mutation carriers it is advisable to avoid hormone replacement therapy, as currently there is no data regarding the effect of the therapy on penetrance of breast cancer susceptibility genes. The same mammographic appearance is seen in BRCA mutation carriers and non-carriers and so a screening mammogram could prove to be effective in BRCA mutation carriers as long as an experienced radiologist can interpret and perform it.

BRCA mutation carriers who do not undergo prophylactic mastectomy require screening recommendations which include breast examination every 6 months and mammography every 12 months beginning at age 25 years. The use of Magnetic resonance imaging (MRI) seems to be beneficial for high risk individuals and known BRCA mutation carriers. MRI has be shown to be more sensitive at detecting breast cancerin younger women with dense breasts (Kriege M, et al; 2004.).The disadvantage is that MRI does not detect benign breast lesions that cannot be easily distinguished from malignancy. This means more false positives, which will lead to more interventions including more biopsies. The American cancer society recommends for annual MRI in women with a 20-25% or greater lifetime risk of developing breast or ovarian cancer and those treated for Hodgkin's disease in their teens or early twenties (Saslow D, et al: 2007.). The use of Tamoxifen has shown a 49% reduction in breast cancer incidence in high risk women. However its uniform use for BRCA carriers is still too early to advocate. Cancers which result from BRCA1 mutations are often high grade and hormone receptor negative. Approximately 66% of BRCA1-associated DCIS lesions are

estrogen receptor negative which suggests hormone-independent phenotype is acquired early. Tamoxifen is more effective at preventing estrogen receptor-positive breast cancers.

Ovarian cancer risk in BRCA1 and BRCA2 mutation carriers is 10 times higher than in the general population and equivalent to 20-40%. A logical prevention option in mutation carriers is Prophylactic oophorectomy. The current recommendation from The American College of Obstetrics and Gynaecology states that prophylactic oophorectomy should be considered at the completion of childbearing or at the time of menopause in women with documented BRCA1 or BRCA2 mutation. Recommendations from the Cancer genetics studies consortium state yearly transvaginal ultrasound timed specifically to avoid ovulation. They also recommend serum cancer antigen 125 annual measurement beginning at age 25 years. The two mentioned recommendations are considered the best screening modalities for ovarian carcinoma in BRCA mutation carriers who have opted to defer prophylactic oophorectomy.

Increased risk of breast cancer can also be associated with other hereditary syndromes such as Cowden disease (PTEN mutation resulting in cancers of thyroid, GI tract and benign skin and subcutaneous nodules), Li-Farumeni syndrome (p53 mutations) and syndromes of breast and melanoma (Figure 9.)

Figure

Table 17-8 Incidence of Sporadic, Familial, and Hereditary Breast Cancer	
Sporadic breast cancer	65–75%
Familial breast cancer	20–30%
Hereditary breast cancer	5–10%
BRCA1 [a]	45%
BRCA2	35%
p53 [a] (Li-Fraumeni syndrome)	1%
STK11/LKB1a (Peutz-Jeghers syndrome)	<1%
PTENa (Cowden disease)	<1%
MSH2/MLH1a (Muir-Torre syndrome)	<1%
ATMa (Ataxia-telangiectasia)	<1%
Unknown	20%

[a]Affected gene.

9. Source: Adapted from Martin.[54]

Several founder mutations have been identified in BRCA1. The two most common mutations are 185delAG and 5382insC, which account for 10% of all the mutations seen in BRCA1. These two mutations occur at a 10-fold higher frequency in the Ashkenazi Jewish population than in non-Jewish whites. The carrier frequency of the 185delAG mutation in the Ashkenazi Jewish population is 1% and, along with the 5382insC mutation, accounts for almost all BRCA1 mutations in this population. Analysis of germline mutations in Jewish and non-Jewish women with early-onset breast cancer indicates that 20% of Jewish women who develop breast cancer before age 40 years carry the 185delAG mutation.

Close Surveillance

In the United States, individuals at high risk for breast cancer are subjected to guidelines established in 2002 by the National Comprehensive Cancer network and the Cancer genetics studies Consortium. The guidelines are based primarily on expert opinion. Screening guidelines are not established by prospective trials.

Another approach may be to target mammography to women at higher risk of breast cancer to improve the balance of risks and benefits. Women in a family with a breast and ovarian cancer syndrome are recommended to have monthly breast self-examination beginning at 18-20 years of age, semi-manual clinical breast examination beginning at age 25, annual mammography beginning at 25 or 10 years before the earliest age at onset of breast cancer in a family member.

Screening mammography when undertaken routinely in women $>/= 50$ years reduces mortality from breast cancer by 33%. This reduction has the advantage of having no substantial risks and being at an acceptable economic cost. Having said that the use of screening mammography in women < 50 years is more controversial due to three main reasons. Firstly mammography at younger age is less likely to detect early breast cancer because breast density is greater. Secondly more false positives are associated with screening mammography which leads to unnecessary biopsies. Thirdly younger women are less likely to have breast cancer and so fewer will benefit.

The benefits of screening mammography in women between the ages of 40-49 years still appear to outweigh the risks. In a study of women aged between 40-49 years, those with family history of breast cancer were 3 times more likely to have an abnormal mammography finding. Studies show, that half the detected breast cancers in women with known BRCA1 or BRCA2 mutations were diagnosed between screening episodes and not during routine screening. For this reason some clinicians recommend an annual screening MRI to

mammography. Individuals with strong family history are offered genetic counselling which includes discussion of genetic testing for BRCA1 and BRCA2 mutations.

A promising strategy for increasing the accuracy of risk assessment models could be to incorporate breast density measurements into the models. Current recommendations for the general population state that women should undergo mammography at age 35 and then have annual mammographic screening beginning at age 40.

Chemoprevention for Breast Cancer

The first drug shown to reduce the incidence of breast cancer in healthy women was the selective estrogen receptor blocker, Tamoxifen which is currently the only drug approved for reducing breast cancer risk. The drug is of special benefit for treatment of estrogen receptor positive breast cancer due to its action as estrogen antagonist.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) in the United States performed a trial of tamoxifen versus placebo. In the breast cancer prevention trial (NSABP P-01) a total of 13 000 randomly assigned women, with 5 year Gail relative risk of breast cancer of 1.70 or higher, received tamoxifen or placebo. Here tamoxifen was shown to reduce the risk for invasive breast cancer by 49% through 69 months of follow-up, with a risk reduction of 59% in the LCIS group and 86% in those with atypical ductal or lobar

hyperplasia. (Fisher B, et al: 1998.). It is worth mentioning however that the reduction in risk was only noted for Estrogen receptor positive cancers.

There were however complications associated with tamoxifen treatment for 5 years. Other findings included deep vein thrombosis occurring 1.6 times as often, pulmonary emboli 3.0 times as often and endometrial cancer 2.5 times as often in women taking tamoxifen With regards to endometrial cancer, the increased risk is restricted to early stage cancers in post-menopausal women.

Cataract surgery was found to be required almost twice as often among women taking tamoxifen. This led, Gail and colleagues to develop of a model that accounts for underlying risk of breast cancer as well as co morbidities to determine the net risk benefit ratio use for chemoprevention (Gail MH, et al: 1999.).

The second chemoprevention trial completed by NSABP compared tamoxifen and raloxifen for breast cancer risk reduction in high risk post-menopausal. The STAR trial (otherwise known as the P-2 trial) of Tamoxifen and Raloxifen, randomly assigned 19 000 postmenopausal women at high risk for breast cancer to receive either tamoxifen or raloxifen. In this study raloxifen was the experimental arm in the follow up prevention trial. Raloxifen's use in managing postmenopausal osteoporosis suggested that it might be even more effective at breast cancer risk reduction, without the unwanted adverse effects of tamoxifen on uterus. The placebo-controlled trials were aimed at finding or proving the efficacy of raloxifene for

prevention and treatment of osteoporosis. At a median followup of 5 years the 2 agents were reported to be nearly identical in reducing the risk of breast cancer, but raloxifene was associated with more favourable adverse event profile (Vogel VG, et al: 2006.). Raloxifene had the added benefit of reducing the number of uterine cancers by 36%, and 29% fewer episodes of venous thrombosis and pulmonary embolism.

The same study (STAR) used 19,747 female subjects who were at increased risk for breast cancer. The subjects received either tamoxifen or raloxifene. Both drugs were shown to reduce the risk of developing breast cancer by 50% with tamoxifen having the added benefit of reducing the incidence of LCIS and ductal carcinoma in situ (DCIS). Raloxifen was not shown to have an effect in the frequency of these diagnoses. No increase in uterine cancer was observed.

Other benefits of tamoxifen include its proven ability to reduce incidence of a second primary breast cancer in contralateral breast. This is apparent in women receiving the drug as adjuvant therapy for a first breast cancer. A study known as the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), adjuvant tamoxifen was shown to reduce the risk for a second breast cancer in unaffected breast by 47%. Currently Tamoxifen therapy is recommended only for women who have Gail relative risk of 1.70 or higher.

Prophylactic Mastectomy

Prophylactic mastectomy was found to reduce the risk of breast cancer in high risk women, by 90% (Hartmann LC, et al: 1999). Women undergoing annual mammograms have an overall 80% chance of surviving occurrence of breast cancer. Mutation carrying women have a penetrance of 50-60% and yet likelihood of death from breast cancer in BRCA1 and BRCA2 mutations is approximately 10%, without undergoing preventative mastectomy (Hartmann LC, Schaid DJ, Woods JE, et al: 1999;).

The effect of prophylactic mastectomy on longterm quality of life is poorly addressed. In a study conducted by Hartmann, a total of 639 women were divided into high-risk (n=214) and moderate risk (n=425) groups, and high risk groups (autosomal dominant family history). The women then underwent prophylactic mastectomy. The Gail model of risk assessment was used for women of moderate risk to find the number of expected breast cancers and 37.4 breast cancers were expected of which only 4 actually developed (An incident reduction of 89%). A different method was used to calculate the expected number of breast cancers in the high risk group. This was due to the fact that the Gail model underestimated the risk in this group. Hence statistical models from a control study of the high risk probands (sisters) were used. Only 3 breast cancers developed after prophylactic mastectomy giving an incident risk reduction of 90%.

A study of women carriers of BRCA mutation showed different benefits of prophylactic mastectomy, according to the risk posed by the mutations. In a prospective study of BRCA1 and BRCA2 mutation carriers, prophylactic mastectomy was compared with surveillance.

Meijers-Hejboer showed that (at 2.9 years of followup), no breast cancer had developed in any of the 76 mutation carriers who underwent preventative mastectomy compared with 8 breast cancers developing in 63 women who opted for surveillance. Prophylactic mastectomy added nearly 3 years of life to women who had with estimated lifetime risk of 40%. In women with an estimated lifetime risk of 85% prophylactic mastectomy added > 5years of life (Schrag D, et al: 1997.)

Another group lead by Scheuer reported no breast cancer in 29 women who underwent mastectomy as oppose to 12 of 165 of high risk women who chose not to have preventative mastectomy. These findings were after 24.2 months of follow-up. Hence the current thinking suggests that a reduction in the risk for breast cancer will translate into survival benefits.

Conclusion (drawing conclusions and implications for practice from the point of view of prevention)

Risk factors for breast cancer are an important tool in providing clues to pathogenesis and identifying patients likely to benefit from surveillance and risk reduction interventions (Figure 10). Although breast cancer can develop in both sexes, women are at greatly increased risk and breast cancer in males is uncommon. Age is a useful risk factor applied everyday in clinical practice; breast cancer is rare in women younger than 30 and very common in women older than 60. Family history is most significant when breast cancer affects young first-degree relatives (mothers, sisters, and daughters) and when cases of ovarian cancer are found within the same side of the family. Histologic risk factors most concerning are ADH (acute ductal hyperplasia), ALH (atypical lobar hyperplasia), and LCIS (Lobar carcinoma in situ).

Figure 10.

Table 34-4 -- Significant Risk Factors for Breast Cancer in Women: Assessment and Recommendations

RISK FACTORS	MAMMOGRAPHY SCREENING RECOMMENDATIONS	PREVENTIVE OPTIONS
Factors Conferring Moderate to High Risk		
Age >60 yr	Annual	Not usually recommended
Atypical hyperplasia (ductal or lobular)	Annual after diagnosis	Tamoxifen, 20 mg/day × 5 yr
LCIS	Annual after diagnosis	Tamoxifen, 20 mg/day × 5 yr
Personal history of either DCIS or invasive cancer, age >40 yr	Annual after diagnosis	No specific preventive recommended [*]
Family history of breast cancer (1st-degree relative, age <50 yr; two relatives on same side of family)	Annual after age 40	Referral for genetic counseling
Factors Conferring Very High Risk		
Therapeutic thoracic radiation (age <30 yr)	Annual at 10 yr after radiotherapy	No specific preventive recommended [*]
Personal history of DCIS or invasive cancer, age <40 yr	Annual after diagnosis	No specific preventive recommended [*]
Family history of breast cancer (two 1st-degree relatives, age <50)	Annual after age 35-40	Referral for genetic counseling
Family history of breast and ovarian cancer (1st-degree relatives)	Annual after age 35-40	Referral for genetic counseling
Known carrier of a mutation in *BRCA1* or *BRCA2* or a 1st-degree relative with a mutation	Annual after age 25; consider annual MRI	Genetic testing for relatives; discuss prophylactic mastectomy or oophorectomy for carriers

DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ; MRI, magnetic resonance imaging.

A personal history of breast cancer predisposes to contralateral breast cancer in women undergoing mastectomy and to bilateral breast cancer in women undergoing breast conservation with wide excision and radiation. These factors are summarized in the table below. The preventative options include mammography, genetic councelling, tamoxifen, and prophylactic mastectomy. The suggestions featured in Figure10. are meant only to guide discussions with patients. Women's preferences and the specific clinical situation are often more complicated

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