Breast Cancer Awareness: How Risk Factors and Screening Methods Impact Detection

by

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ABSTRACT

The purpose of this paper is to create awareness around breast cancer risk factors and screening methods. Five overarching intrinsic risk factors, including: the patient's age at the time of diagnosis, race, familial susceptibility, and the role of natural hormone changes, and one extrinsic risk factor, dietary habits, were selected for consideration. Along with risk factors, four screening methods were taken into consideration. These included self-breast exams, mammograms, magnetic resonance imaging (MRI), and ultrasound. The recommendation of screening methods was then determined in relation to a women's risk for breast cancer. Two categories of risk (average and high risk) were defined and the recommended screening methods were determined based on the risk. Overall, mammography was found to be a useful tool in both average and high risk women. For high risk women, mammography with MRI had a greater sensitivity and was able to detect more breast cancers. More research needs to be conducted on the efficacy of Breast MRI, Ultrasound, and breast self-exams as supplemental tools to mammography in both average and high-risk women.

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CHAPTER 1

INTRODUCTION

In 2020, the World Health Organization determined breast cancer to be the most common cancer diagnosed with 2.26 million cases (WHO, 2022). Specifically, breast cancer is the most common cancer for U.S. women and is the second leading cause of cancer-related death among women after lung cancer (DeSantis et al, 2019). Additionally, the risk of breast cancer remains prevalent as the same study conducted by DeSantis (2019) from 2012-2016 found that the incidence rate continued to increase by 0.3% each year. Due to the prevalence of breast cancer amongst women, it is necessary to compile information regarding risk factors and diagnostic techniques to understand how these impact detection. Therefore, this review will explain the various risk factors that have been identified (age, race, familial susceptibility, hormonal factors, and dietary factors), diagnostic techniques (mammogram, self-breast exam, breast MRI, and ultrasound) and their harms and benefits, and ultimately the impact on detection of breast cancer specifically for women.

CHAPTER 2

TYPES OF BREAST CANCER

Breast cancer can be differentiated by the kind of cells in the breast that become cancer. Due to there being different kinds of breast cancer, the risk factors, screening methods, and treatment plans will vary based on the type of cancer diagnosed. Detection of breast cancer hinges on the knowledge of risk factors and awareness. The American Cancer Society[1] (2021) divides breast cancer into three groups: ductal or lobular carcinoma, special types of invasive breast cancers, and less common types.

Ductal carcinomas form in the lining of a milk duct within the breast. Lobular carcinomas grow in the lining of the milk producing glands of the breast. Within the ductal or lobular carcinomas, there is the ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS). Both DCIS and LCIS do not spread past where they originated. DCIS stays within the milk duct and LCIS stays within the walls of the lobules. Ductal and lobular carcinomas can be invasive. Invasive ductal carcinoma (IDC) is the most common type of breast cancer (70-80% of cases) and will spread into the surrounding breast tissue.

Special types of invasive breast cancers encompass triple-negative or basal-like and inflammatory breast cancer. With triple-negative breast cancer, the cancer cells do not have estrogen or progesterone receptors (ER or PR), nor do they make the protein HER2, which controls the growth rate of breast cancer. This accounts for about 15% of breast cancers. Inflammatory breast cancer blocks lymph vessels in the skin, which causes the breast to look inflamed. This kind of cancer accounts for 1-5% of diagnosed breast cancers.

The less common types of breast cancer include: Paget disease of the breast, angiosarcoma, and phyllodes tumor. Paget disease of the breast is rare and only accounts for 1-3% of all breast cancer cases. It starts in the breast ducts and spreads to the nipple and areola. Angiosarcoma makes up less than 1% of all breast cancer and it starts in cells that line blood vessels of lymph vessels. It can involve the breast tissue or skin and could potentially be related to previous radiation therapy. Phyllodes tumors develop in the connective tissue of the breast (American Cancer Society[1], 2021).

Breast cancers can also be split into groups based on their genetic information. Group 1, or Luminal A, includes tumors that are Estrogen Receptor (ER) positive and Progesterone Receptor (PR) positive, but are negative for the HER2 gene. The HER2 gene produces too much of the growth-promoting protein that is called HER2. Group 2, or luminal B, includes tumors that are ER positive, PR negative, and HER2 positive. Group 3, or HER2 positive, are ER and PR negative, but HER2 positive. Group 4, or basal-like, are known as triple-negative breast cancer, which are ER, PR, and HER2 negative (Mayo Clinic, 2022).

While new cases of breast cancer still arise and the incidence rate is slowly climbing, the mortality rate has decreased due to early detection (Wang, 2017). The next sections will discuss risk factors of breast cancer and different screening methods to detect breast cancer. The final section will discuss how risk factors play a role in the screening methods used for women.

CHAPTER 3

BREAST CANCER RISK FACTORS

There are many factors that can lead to the abnormal growth of breast tissue (Welsh, 2017) and with breast cancer being one of the most common diseases of mortality in the United States, the risk factors of this disease have been greatly researched. Kaminska et al. (2015) found the most pertinent risk factors are age over 40, history of mammary gland diseases, history of cancer in first-degree relatives, early menarche and late childbearing, woman's age at menopause, and race. These were divided into the categories of intrinsic and extrinsic risk factors. Intrinsic factors include the patients' age at the time of diagnosis, race, familial susceptibility, and the role of natural hormone changes that take place in the period of maturation. The extrinsic factors have been detailed as dietary habits. Because there are a multitude of risk factors that are interconnected, this paper will detail these particular and most common risk factors.

3.1 Age at Diagnosis and Survival

Breast cancer incidence can be divided by age group to determine the age with the highest risk for breast cancer. According to Giaquinto's *Breast Cancer Statistics* (2022), the age group with the highest diagnosis or incidence of breast cancer is those 60-69 years old. Those who are 20-29 years old account for the lowest incidence of breast cancer. The table below configures Giaquinto's (2022) breast cancer incidence in relation to age group.

Table 1: This table configures the breast cancer diagnosis or incidence by age group from Giaquinto's (2022) breast cancer statistics study.

Age Group (years)	Breast Cancer Incidence
20-29	1%
30-39	4%
40-49	13%
50-59	22%
60-69	29%
70-79	21%
<80	11%

The age of diagnosis of breast cancer may contribute to someone's prognosis or survival of the disease. The chance of survival can be broken down into age groups. Adami et al. (1986) had age groups: < 30, 45-49, 50-59, and the oldest women >75 years. In this study, those aged 45-49 at diagnosis had the highest survival rate or most favorable prognosis. Those that were 5 to 10 years older, 50-59 years old at diagnosis, had a survival rate that was 10-15% lower than the previous age group.

The youngest patients, those who were less than 30 years of age, had a lower survival rate than the 45–49-year-olds by 7.6-12.9%, which is slightly less than the oldest age group. This study hypothesizes that the 45-49 age group had the highest survival rate due to this age coinciding with the mean age of menopause being 49. As these hormones deplete, the growth rate of the tumors would decrease. However, hormonal stimulation may not be the only factor contributing to age-related survival differences, and is specifically confounded by the clinical stage at which the cancer is diagnosed.

Kroenke et al. (2004), found that young women experience more loss of physical function (mean change in health-related quality of life) than middle aged women. In this study, 122,969 women, ranging from 29-71 years of age, responded to pre- and post-functional status assessments. The responses were categorized into the following age groups: <40, 41-64, and >65 years. Those less than 40 years old experienced the largest decline of health-related quality of life, specifically in bodily pain, mental health, and social functioning, compared to the 41-64 age group. Those older than 65 attributed much of the decline in their health-related quality of life to their age and not their breast cancer prognosis.

A third study, conducted by Brandt et al. (2015), confirmed the results of the two previously discussed studies. Those under the age of 40 and over the age of 80 had a poor prognosis and statistically higher 10-year mortality rate. The poor prognosis for women under 40 had the strongest association with axillary lymph node negative breast cancer. However, those over 80 years old had a poor prognosis that was independent of stage of cancer at diagnosis. Hormonal factors could play a role in survival rate at different ages, which will be further discussed in a later section.

3.2 Race as a Risk Factor

Ghafoor et al. (2003) found that cancer incidence rates have increased among women of all races combined. Specifically, the rate has increased in white women by 0.4% per year from 1987-2000, and predominantly involves small and localized stage tumors. The incidence rate of African American women stabilized in the 1990s for all breast cancers and for localized tumors. African American women are more likely than white women to be diagnosed with a large tumor (> 2cm) and distant stage disease. White and African American women have a higher incidence rate for breast cancer than other racial or ethnic groups. The incidence rates for other racial or ethnic groups is found below in Table 2.

Table 2: This table gives the average annual incidence rate from 1996-2000 per 100,000 cases in relation to Race (Ghafoor, et al., 2003).

Race	# of cases per 100,000
White	140.8
African American	121.7
Asian American/Pacific Islander	97.2
Hispanics	89.8
American Indians/ Alaska Natives	58

While white and African American women experience a higher incidence rate than other racial or ethnic groups, African American women have a lower incidence rate than white women. However, African American women experience a higher mortality rate from breast cancer than white women. Socioeconomic factors probably account for the disparities in breast cancer outcomes among the races. The poverty rates, lacking medical insurance, and reliance on public insurance is twice as high for African Americans as it is for white Americans (Newman, 2005).

There is a significant difference in the impact that risk factors have on African American women, compared to others. More specifically, family history and age at menarche are more prevalent risk factors. There was also a difference in the age of onset of the disease. African American women under the age of 45 have a higher incidence than white women of the same age group. As both groups reach the age of 50, white women's incidence increases past African American incidence (Ries, 2003).

Hunter et al. (1993) examined the factors associated with the stage of the cancer. In this particular study, the population of the study was 649 African American women and 573 white women. It was found that there were indicators of differences in access to health care, a lack of mammograms, and an increased body mass index that contributed to different stages of cancer in the African American population. However, it was also found that no single factor or group of factors can explain the race-stage differences. Other studies have also looked into how race contributes to survival and morbidity of breast cancer. In 2002, Campbell performed a literature review and found that African American and lower income women were consistently shown to have a more advanced disease at diagnosis than white women and would benefit greatly from early detection. Also, it was found that the survival rates for whites are higher than for African Americans at each stage of the disease (Eley et al., 1994). DeSantis et al. (2019) found that the mortality rate for African American women is 40% higher than white women, even though the incidence rate for African American women is lower.

Different types of breast cancer also appear at different rates based on race and menopause. A study conducted in 2006 by Carey et al. found that basal-like tumors were more prevalent in premenopausal African American women than postmenopausal African American and non-African American women. Pre- and post-menopausal factors in breast cancer will be discussed later on.

3.3 Familial Susceptibility

3.3.1 First and Second Degree Relative and Incidence

Having a first or second degree relative that was diagnosed with breast cancer can increase a woman's risk of being diagnosed as well. Sattin et al (1985) investigated a person's family history and its impact on the risk of getting breast cancer. They looked at the relationship between a first degree and second degree relative and the incidence of breast cancer. In this study, it was found that women with no family history had the lowest risk and those who only had a first degree relative had the highest risk. Those with a first- and second-degree relative had about the same, but slightly lower risk, as those with a first-degree only relative. The data from Sattin et al.'s (1985) study is listed in the table below.

Table 3: This table depicts the data of relative risk in relation to family history (Sattin et al., 1985).

Family History	Relative Risk
None	1.0
First-degree only	2.3
Second-degree only	1.5
First- and Second-degree	2.2

Along with looking at first- and second- degree relatives, Sattin et al. (1985) looked more specifically at mother and sister breast cancer history in relation to risk. It was found that having both a mother and sister, who were diagnosed with breast cancer, increased the risk by 6.5 times when compared to having only a mother or only a sister who had been diagnosed with breast cancer. The data for these relationships are configured in the table below.

Table 4: This table shows the family history in regards to having a mother or sister that was diagnosed with breast cancer and the relative risk that poses.

Family History	Relative Risk
Mother	2.1
Sister	2.1
Both mother and sister	13.6

More recently, a study was conducted by Shiyanbola et al. (2017) that would continue to place an importance on first-degree family history as a risk factor for breast cancer. In this study, it was found that women with a first-degree family history of breast cancer increased overtime and by age. From these studies, it can be concluded that women with a first-degree relative have a higher risk for breast cancer.

3.3.2 BRCA1/2 Role in Cancer

BRCA is the abbreviation for Breast Cancer gene. In its original function, BRCA is a tumor suppressor gene; it provides instructions for making a protein that suppresses the making of tumors. The BRCA protein helps repair damaged DNA, so that do not divide rapidly or in an uncontrolled way, unless the gene is mutated. Specifically, mutations in the gene are what are oncogenic and breast or ovarian cancer causing. The average cumulative risk for patients that are carriers for the BRCA1 mutation is 65% risk of breast cancer by the time they reach 70 years of age. For the BRCA2 mutation carriers the risk of breast cancer is 45%. They were also able to determine that the risk for breast cancer declined with age for those carrying the BRCA1 mutation. However, for those carrying the BRCA2 mutation, there is a higher risk for breast cancer that is diagnosed after the age of 35 (Antoniou et al., 2003).

Other studies have been performed in order to determine the risk of cancer that are caused by both the BRCA1 and BRCA2 mutations. BRCA mutations can also contribute to contralateral breast cancer. Contralateral breast cancer is when a new tumor appears in the opposite breast from the original diagnosis, 6 months prior. Unilateral breast cancer is when cancer is only developed in one breast. Begg et al.'s (2008) study determined the risk of carrying the BRCA1 or BRCA2 mutation and the risk of getting cancer. They were able to observe a statistically significant trend of increasing risk with the decrease of age when a proband is diagnosed. They saw that risks in relatives of contralateral breast cancer probands are at a higher risk than relatives of unilateral breast cancer probands (2008). Begg et al.'s (2008) results are also aligned with Antoniou et al.'s (2003) results. In that study, the authors pooled together pedigree data from 22 studies that included 8,138 case patients. Breast and ovarian cancer incidence rates were determined using a modified segregation analysis.

Graeser et al. found that there is a 47.4% risk for contralateral breast cancer 25 years after the first diagnosed breast cancer for patients whose families have BRCA1 and BRCA2 mutations (2009). Those with the BRCA1 mutation had a 1.6 fold higher risk of contralateral breast cancer than those with the BRCA2 mutations. Overall, this study found that contralateral breast cancer risk depends both on age and on a mutated BRCA gene. There is significant risk of developing contralateral breast cancer if the patient is a BRCA1/2 mutant carrier, or has a family history of BRCA1/2 mutation. This risk increases if the patient is relatively young when first diagnosed (less than 41 years of age).

3.4 Hormonal Factors

There are multiple studies that look into the relationship between the time of reproduction, menopause, and when breast cancer is diagnosed. This is due to hormone-mediated factors that are strongly suspected of being related to breast cancer. Several endocrine glands and the hormones produced by these glands influence the development of breast tissue (Begg et al., 1987). Common factors observed for hormonal risk to breast cancer include: age at menarche, age at first birth, and postmenopausal breast cancer. These topics will be discussed in the following sections relating to hormonal risk factors.

3.4.1 Age at Menarche

There are a few determinants of the age at menarche. Increased height and body mass index can accelerate the occurrence of menarche. Opposed to this, moderate physical activity and an increased total energy intake can be associated with a delay in age at menarche (Petridou et al., 1996). The Collaborative Group on Hormonal Factors in Breast Cancer determined that early menarche can increase breast cancer risk. In this review, data from 117 epidemiological studies, which included 118,964 women with invasive breast cancer and 306,091 women without breast cancer were considered. From this, it was found that the risk for breast cancer increased by a factor of 1.050 for every year younger at menarche (2012). Clavel-Chapelon and Gerber (2002) found that there is a 9% decreased risk of breast cancer with the increasing age of menarche. Both studies concluded that the younger age of menarche led to a higher risk of breast cancer.

3.4.2 Age at Menopause

The NIH's National Institute of Aging defines menopause as "a point in time twelve months after a woman's last period" and often begins between ages 45-55 years old (2021). One study looked at the association between reproductive factors and risk of premenopausal breast cancer for women who were less than 40 years old and compared that to women who were older than 40 and premenopausal. There were more cases for those who were younger than 40 and premenopausal. It was found that tumors were larger in size, higher grade, and hormone receptor negative than in older women (Warner et al., 2013).

Another study, conducted by Trichopolous et al. (1972), found that the relative risk of breast cancer increased with age at natural menopause. The women who had natural menopause occur at age 55 or older had twice the risk of breast cancer than those whose menopause occurred before the age of 45. The risk was reduced by one third for those who had menopause induced before the age of 35. The greatest risk for breast cancer was associated with those that had a late and natural menopause after age 70. These studies both show that earlier menopause, be it natural or induced, can reduce the risk of breast cancer; while they also show that later menopause can increase the risk of breast cancer.

3.4.3 Age at First Birth/Pregnancy

Clavel-Chapelon and Gerber (2002) also found that breast cancer risk increased by 5% as the age of the first full term pregnancy increased; however, each full term pregnancy led to a 3% decreased risk of breast cancer when cancer was diagnosed before menopause. Chie et al. (1999) state that the earlier age at first full term pregnancy is inversely related to breast cancer risk, meaning that breast cancer risk is lower for those younger during their first full-term pregnancy. A late age for a last full-term pregnancy has also been linked to a higher risk of breast cancer. MacMahon et al. (1970 & 1982) found that women having their first child under the age of 18 and then under the age of 20, respectively, have one third of the risk of breast cancer than those who wait to have their first child after the age of 35 years or did not have a child at all.

A meta-analysis performed by Ewertz et al. (1990) found that women, who had never given birth, had a 30% increased risk compared to women who had children. Also, for every two births, the risk decreased by 16%. For those who had children after the age of 35, their risk of breast cancer increased by 40% when comparing them to women who gave birth for the first time before the age of 20. These studies clearly demonstrate the risk factor for age at first full-term pregnancy. Those who have their first pregnancy at a younger age will have a lower risk for breast cancer.

3.5 Dietary Habits

There are a few avenues that can be taken when considering how dietary habits impact breast cancer. Studies have considered the aftermath of dietary habits leading to obesity and its ability to cause breast cancer. Some studies have considered specific dietary nutrients, such as saturated vs unsaturated fats, cholesterol intake, and linoleic acid and have associated it with: being the cause of breast cancer, limiting the risk of breast cancer, and decreasing the ability of survival post the removal of breast cancer. This section aims to detail the most common topics of dietary habits and their impact on breast cancer incidence.

3.5.1 Obesity

Along with the age of diagnosis playing a factor into the risk of breast cancer, obesity can also contribute to an increased risk of premenopausal and postmenopausal breast cancer. Anderson and Neuhouser (2012) found that there is a strong significance of increased risk of premenopausal breast cancer in people who are overweight. However, they found that there was a statistically nonsignificant increased risk of postmenopausal breast cancer in people with obesity. Excess body weight and obesity have been linked to postmenopausal breast cancer (Ligibel, 2011). A higher BMI has also been associated with a more advanced stage of breast cancer at diagnosis. It is thought that the increased BMI is associated with a lifetime exposure of estrogen. Estrogen plays a role in the initiation and progression of breast cancer lesions. This association was stronger in women younger than 50 years when compared to those older than 50 years (Carmichael and Bates, 2003).

Other studies have linked obesity and breast cancer risk on a molecular level. Brown and Simpson (2010) found that the regulation of aromatase expression in the breast by AMPK, which regulates cellular metabolism, and CRTC2, in response to the altered adipokine milieu that is associated with obesity can provide that important link.

3.5.2 Cholesterol Intake

Cholesterol intake potentially has an impact on breast cancer. Evidence indicated that cholesterol is capable of regulating proliferation, migration, and signaling pathways in breast cancer (Danilo and Frank, 2012). Hu et al. (2012) has evidence to support that dietary cholesterol was positively associated with the risk of mostly postmenopausal breast cancer.

There is a negative association between a five-year disease-free survival from breast cancer and the combination of high serum cholesterol levels and high weight; while there is a positive association between a five year disease free survival and low serum cholesterol and low weight. In this study, Tartter et al. (1981) analyzed the disease free survival rates of 374 women with operable breast cancer. They found that preoperative weight with the combination of serum cholesterol plays a large role in determining the survival rate and living disease free for 5 years post operation.

It is thought that 27-hydroxycholesterol (27HC) influences breast cancer. This metabolite can function as an estrogen, which would increase the proliferation of estrogen receptor positive breast cancer cells (Nelson et al., 2014). This was further demonstrated in Luo et al.'s (2022) study when they found that 27HC is the most abundant oxysterol that increases the risk of breast cancer progression. This is done by the histone reader, ZMYND8, which is a master transcriptional regulator of 27HC metabolism. By ZMYND8 boosting the transcription of 27HC, it led to 27HC accumulating in breast cancer stem cells, which then led to the 27HC promoting oncogenic transformation. Overall, cholesterol impacts cell signaling and metabolism of cells. When there is an increase in cholesterol intake, this can promote more proliferation in breast cells, which can increase the risk of breast cancer.

3.5.3 Saturated/Unsaturated Fatty Acids

The difference between saturated fats and unsaturated fats is in their structure. Saturated fats lack double bonds between their carbon atoms. Saturated fats can also contribute to "bad" cholesterol, which means they contain low density lipoprotein (LDL). Unsaturated fatty acids have high density lipoprotein (HDL), which is considered "good" cholesterol because it is taken to the liver, where it can be broken down. Conversely, LDL is not broken down and can build up in the arteries. Because of this, saturated fatty acid intake has a positive association with postmenopausal breast cancer risk (Xia et al., 2015). A meta-analysis looked into total fat intake along with meat intake and saturated fat intake. When combining total and saturated fat intake with total meat intake, there was an association between higher intakes and increased risk of breast cancer (Boyd et al., 2003).

3.5.4 Linoleic Acid

Linoleic acid is an essential nutrient that the body must consume and cannot make on its own. It is most commonly found in nuts and seeds. Many reviews have been done to determine if linoleic acid has an effect on breast cancer risk. In 2009, Aro et al. determined that conjugated linoleic acid (CLA) was anticarcinogenic and that a diet rich in CLA could protect against breast cancer in postmenopausal women. Years later, Zhou et al (2015) determined that dietary and serum CLA could decrease the risk of breast cancer. The means by which conjugated linoleic acid decreases the risk of breast cancer is by blocking estrogen signaling in human breast cancer cells (Tanmahasamut et al., 2004). In this study, CLA was found to downregulate estrogen receptors alpha (ERα) at the mRNA and protein levels. This led to the conclusion that CLA possesses antiestrogenic properties that could account for their antitumor activity on breast cancer cells.

3.6 Conclusion

In this section, a multitude of risk factors, both intrinsic and extrinsic, were considered for breast cancer. The probability of survival at the age of diagnosis was found to increase for those under the age of 40 and those over the age of 80 years old. Race as a risk factor was also considered and it was found that African American women have a higher risk of getting late-stage breast cancer. After this, family susceptibility was taken into account. Women with a first-degree relative have a higher risk of breast cancer compared to those with no family history. There was a higher risk for those with the BRCA1 mutation in getting breast cancer than those with the BRCA2 mutation. However, there was a higher overall risk for those with the BRCA mutations than those without. Then, hormonal risk factors were taken into account through the viewpoint of age at menarche, age at menopause, and age at first full-term pregnancy. There is an increased risk of breast cancer for those with an early age menarche. There is lower risk of breast cancer both for an early age, before the age of 35, first full-term pregnancy and menopause. The last risk factor was dietary habits. This was separated into obesity, cholesterol intake, saturated and unsaturated fatty acids, and linoleic acid intake. Increased obesity, cholesterol intake, and saturated fatty acid intake all led to an increased risk in breast cancer. An increased consumption of unsaturated fatty acids and linoleic acid both had the opposite effect and are able to decrease the risk of breast cancer. After considering all of these risk factors, women should be directed to a screening method that is helpful to them and will help with early detection based on their risk factors.

CHAPTER 4

BREAST CANCER SCREENING METHODS

From the risk factors, it can be seen that age plays a large role in breast cancer risk, survival rate, and getting breast cancer. After breast cancer is detected, the stage of the disease can be determined. The American Cancer Society$_2$ (2021) defines staging as how far the cancer has spread and "how much cancer is in the body". The earliest stage is stage 0, which is also known as carcinoma in situ. Then, the stages range from stage I through stage IV. A pathological or surgical stage is determined by examining the tissue that is removed during an operation. If surgery is not possible or an option, a clinical stage is determined by physical exam, biopsy, and images. Screening for breast cancer can lead to early detection, which increases the survival rate and can lead to detection of a lesser stage (Wang, 2017; Duggan et al., 2021). Early detection of breast cancer can be achieved by screenings with both clinical and self-examination (Strax, 1989). These screenings or examinations can be categorized as preventative measures. The screening methods that will be discussed are: mammography, breast self-examination, MRI, and ultrasound.

4.1 Preventative Measures Grading Systems

The U.S. Preventive Services Task Force (USPSTF) communicates different grades of preventative measures to clinicians to inform on what tests are beneficial and should be recommended to patients. The grades are given based on the level of certainty, which is the "likelihood that the USPSTF assessment of the net benefit of a preventive service is correct" (U.S. Preventive Services Task Force, 2018). The net benefit, in this case, is defined as the benefit minus the harm of the preventative service that is implemented. The USPSTF provides a table further defining the levels of certainty, which is below.

Table 5: This table is from the USPSTF Grade Definitions and describes the level of certainty regarding net benefit.

Level of Certainty*	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as: • The number, size, or quality of individual studies. • Inconsistency of findings across individual studies. • Limited generalizability of findings to routine primary care practice. • Lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of: • The limited number or size of studies. • Important flaws in study design or methods. • Inconsistency of findings across individual studies. • Gaps in the chain of evidence. • Findings not generalizable to routine primary care practice. • Lack of information on important health outcomes. More information may allow estimation of effects on health outcomes.

Based on the level of certainty in regards to the net benefit, a preventative service then receives a letter grade. There is moderate to high certainty that this service provides no net benefit or the harms outweigh the benefit. If the service has an I rating, then there is insufficient evidence to assess the balance of benefits and harms. The table below provides the full description of the USPSTF grading scale for preventative services.

Table 6: This table gives the grade, the USPSTF definition of the grade, and their suggestions for practice.

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	*Note: The following statement is undergoing revision.* Clinicians may provide this service to selected patients depending on individual circumstances. However, for most individuals without signs or symptoms there is likely to be only a small benefit from this service.	Offer or provide this service only if other considerations support the offering or providing the service in an individual patient.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I Statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

These tables will be helpful in determining the benefits, harms, and efficacy of the screening methods described. They will also help to determine which screening methods should be recommended to women based on their risk. So far, the highest grade mammography has received is a grade B, while other age groups have received a C grade. The other screening methods are considered supplemental and have an I grade.

4.2 Mammography

4.2.1 How Mammography is Performed

One of the more common screening tools is a mammogram. The CDC defines a mammogram as an X-ray picture of the breast. A 2-dimensional mammogram is performed by standing in front of an X-ray machine and placing the breast on a plastic plate. Another plate will firmly press down on the breast from above. The steps are repeated to make a side view of the breast and both breasts will be X-rayed the same way (CDC, 2022). The American Cancer Society (2022) describes 3 dimensional mammograms as being similar to 2D mammograms. The only difference is that the machine takes many low dose x-rays as it moves in a small arc around the breast. A computer will put the images together into a series of thin slices. Figure 1 below shows the difference between 2D and 3D mammogram images (United Health Services, 2023).

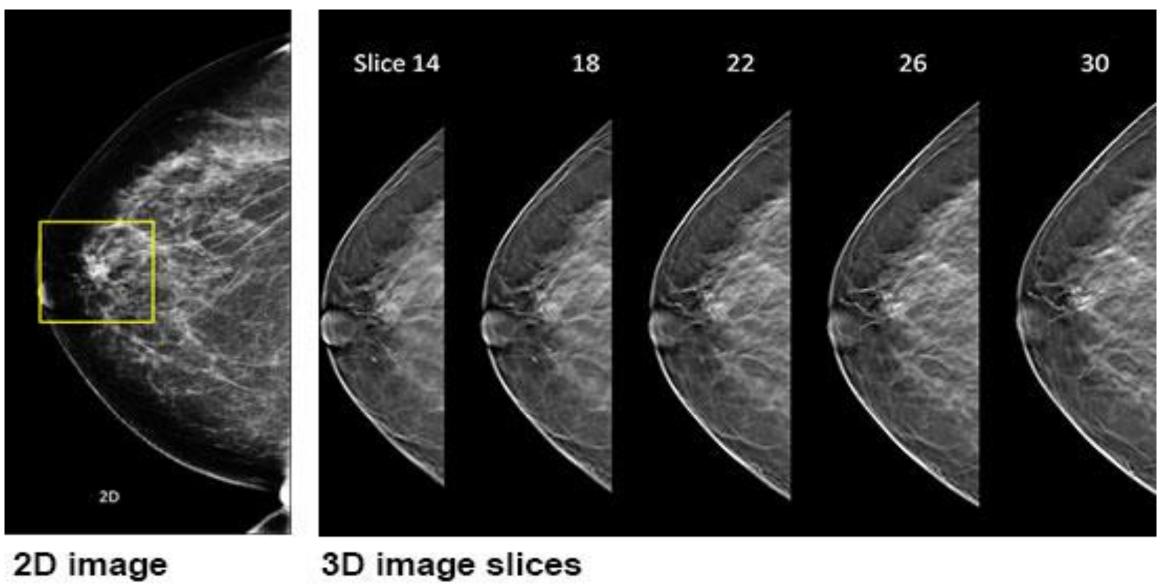

Figure 1: This figure shows the difference between a 2D mammogram (left) and 3D mammogram (right). The 3D mammogram has more sliced images that are put together on the computer and this figure depicts the numbered slices next to each other.

4.2.2 When to Get a Mammogram

The USPSTF (2016) recommends that women aged 50 to 74 should have a mammogram every 2 years. The biennial screening by mammography for this age range has a B grade, meaning that the net benefit is moderate. However, the decision to start testing at an earlier age, like 40-49, is an individual decision that can be made based on one’s own risk factors. The grade for mammography within this age range is a C. The individual who places a higher value on the potential benefit than potential harms would use this screening method earlier on in life. Due to the recommendation of getting a mammogram at an earlier age laying more heavily on the individual's value of potential benefit versus potential harm, it is important to have an understanding of what the benefits and harms of mammography are.

A study was conducted to determine the benefits and harms of mammography screening done annually, biennially, or triennially based on age. The age ranges were 45-49 years, 50-59 years, and 70-74 years. For those who were 50-69 years old, annual screening compared to biennial screening may have had some small additional benefit; however, there was an increase in false positive results for annual screening. Triennial screenings did not show to be more beneficial than biennial screenings for this age group. For those who were 45-49 years old, annual screening provided smaller incremental benefits (number of avoided deaths by breast cancer), but also saw an increase in harm (false positive results) compared to the women aged 50-65. For those in the 70-74 age group, it was found that longer intervals between screenings could be favorable, however there was no significant balance of benefits and harms for the longer interval of screening. Overall, annual screening saw more false-positive test and biopsy results, while biennial screening had lower probabilities of false positives (Canelo-Aybar, et al., 2021). This study supports the USPSTF suggestion to get biennial screening for women aged 50-74 years, however this still leaves women aged 49 and below to a greater risk of overdiagnosis and false positive results, even if they participate in biennial screenings. The harm of overdiagnosis and false positive results will be discussed later on.

4.2.3 Benefits of Mammography

According to the CDC (2022), having regular mammograms can decrease the risk of dying from breast cancer. The United States Preventive Services Task Force (2016) found that of all the age groups, those who are 60 to 69 years are most likely to avoid death by breast cancer through mammography screening. More research needs to be done to determine why this age group benefits the most from mammography. However, a possible reason is because the incidence of cancer goes up as women age, so mammography benefits this group the most by being a means of early detection.

Another review looked at benefits of mammography and determined that the primary benefits are a reduction in mortality and years of life lost. This study determined that the expansion of the screening age range and an increasing the frequency would lead to an increased reduction in breast cancer mortality by 40% for ages 40 to 84. It was also determined that the number needed to screen (NNS) to prevent one breast cancer death decreases with age, because the incidence of breast cancer increases with age. The table below shows the findings of the NNS based on age.

Table 7: This table configures data from Grimm et al.'s (2022) review on the benefits of mammography in regards to reduced mortality. It shows the number of women that need to be screened in order to prevent one death from breast cancer by age group.

Age Group (years old)	Number Needed to Screen (# of women)
40-49	753
50-59	462
60-69	355

In the same study, the years of life lost due to breast cancer were found to be reduced for those who underwent screening. One year of life was gained for every 20 women in their 40's who undergo annual screening, while 45 women in their 70's need to be screened biennially in order to gain one year of life. The reason for this is because mortality benefits of screening younger women are greater due to the longer life expectancy compared to older women (Grimm et al. 2022).

4.2.4 Harms of Mammography

Grimm et al. (2022) also reviewed the harms of mammography, which the most prevalent included: false-positives, anxiety, and radiation injury. False-positives can be split into two groups: false-positive recalls, where a woman is recalled for additional images to evaluate a questionable area, and false-positive biopsies, where a woman gets a biopsy and only benign tissue or atypical cells are found. Age can play a role in false-positive recall rates and it was found that women who start annual screening at age 40 will have 1 false-positive recall every 10 years, while those who start at age 50 will have 1 false-positive recall every 11.5 years. For false-positive biopsy, it was found that approximately 15% of women who undergo a diagnostic exam after a screening recall will be recommended for a biopsy and about one quarter of these biopsies will detect cancer. The rest will be considered false-positive biopsies. Canelo-Aybar et al., (2021) looked into false-positive results and biopsies in relation to age group and the intervals of screening. The tables below show the percent of women who received a false-positive result and false-positive biopsy.

Table 8: This table organizes the data given by Canelo-Aybar et al. (2021) for the percent of women with false-positive results on their mammogram in relation to how often they were screened.

Percent of Women Who Received False-Positive Result			
	Screening Interval		
Age Group (years)	Annual	Biennial	Triennial
45-49	11.2%	6.0%	*
50-59	55.2%	35.4%	24.8%
70-74	47.0%	26.6%	*

* Data not provided

Table 9: This table organizes the data given by Canelo-Aybar et al. (2021) for the percent of women with false-positive biopsies in relation to how often they were screened.

Percent of Women Who Received False-Positive Biopsy			
	Screening Interval		
Age Group (years)	Annual	Biennial	Triennial
45-49	11.4%	5.9%	3.9%
50-59	9.7%	5.4%	3.7%
70-74	9%	4.0%	*

* Data not provided

Overall, this data shows that annual screening can be more harmful in terms of false-positive results and biopsies. Biennial and triennial screening have a lower rate of false-positive result and biopsy incidence.

Anxiety is another harm that can follow from a screening recall or biopsy due to the possibility of breast cancer. Qualitative studies have also determined that women suffer from anxiety after experiencing false-positive results (Health Quality Ontario, 2016). There can also be injury from the radiation used in mammography, because it is an x-ray. Grimm et al. (2022) points out that there are federal laws that set a regulatory limit of radiation for each mammogram and that the risk of developing a fatal radiation-induced breast cancer after undergoing annual mammography from age 40-49 is very low.

Another study cast doubts on mammography when it found that the mortality from breast cancer was not reduced for women who had consistent mammograms (Miller, 2014). This particular study looked at 3,250 women who underwent mammography screening and 3,133 women who did not undergo mammography screening over a 5-year period. After these 5 years, it was found that 500 women who underwent mammography screening and 505 women who did not have mammograms died of breast cancer. The overall mortality was similar between the two groups. Then, after 15 years of follow-up, it was found that an excess of 106 cancers were diagnosed in the mammography group, which was a result of overdiagnosis. These studies show that mammography can lead to overdiagnosis and do not necessarily decrease the death rate of breast cancer. A way to limit the overdiagnosis from mammography and the false positive test results is to educate women on their risk factors and other screening methods they have.

4.3 Breast Self-Exam

4.3.1 How to Perform Breast Self-Exams

Another method of screening women should be educated on is performing their own breast exam. Self-breast exams (BSE) can be performed using three different levels of pressure: light pressure, which allows women to feel the tissue closest to the skin, medium pressure, in order to feel a little deeper, and firm pressure, which allows women to feel deeper breast tissue closer to the chest wall (Logansport Memorial Hospital, 2022). Along with three different pressure types, the American Breast Cancer Foundation (2023) detailed using the pads of the three middle fingers to perform three different patterns of examination: circle, lines/vertical, and wedge. In the circle pattern, one will begin at the top of the breast and move one's fingers slowly around the outside in a large circle. When the circle has been completed, move fingers slightly closer to the nipple and make a smaller circle. Continue making smaller circles until all of the breast tissue has been examined. In the lines/vertical pattern, one will begin in the underarm area. Slowly move fingers down until they are below the breast, then move closer towards the nipple and slowly go back up. Perform this up and down pattern all the way across the breast. Finally, in the wedge pattern, begin at the outside edge of the breast and work fingers towards the nipple. Continue doing one wedge-shaped section at a time until the entire breast has been examined.

4.3.2 When to do Self-Breast Exams

The American Breast Cancer Foundation (2023) suggests that women should start examining their own breasts around the age of 20 years old. This would allow women to become familiar with how their breasts look and feel and create a baseline for them. It is suggested that the exam be performed once a month and for those still menstruating, it is suggested to perform the exam 3-5 days after a period (Mount Sinai, 2022). For those who have gone through menopause, it is suggested to do the exam around the same time every month.

4.3.3 Benefits and Harms of BSE

There is a lot of debate surrounding breast self-exams and whether or not they should be used as a screening method. When a study done by Weiss (2003) looked at breast self-exams, it was determined that there is an uncertainty on whether or not BSE has any effectiveness in reducing breast cancer mortality. Mayo Clinic would agree with Weiss' findings and points out that a lot of medical organizations do not recommend routine breast self-exams as part of breast cancer screening due to self-exams not showing to be effective in detecting cancer or improving survival for women who have breast cancer. A few risks discussed were: anxiety caused by finding a lump, additional tests and procedures that may be necessary to check out lumps or changes, and overestimating the benefits of self-exams. A BSE is not a substitute for a clinical breast exam performed by a doctor or a mammogram (2023). A study performed by Kosters and Gotzsche (2003), found that there was not a beneficial effect from breast self-exam, but an increase in harms. There was an increase in the number of benign lesions that were identified and an increased number of biopsies performed. Based on this information, breast self-exams could not be recommended.

In a study evaluating the efficacy of self-breast examination for breast cancer prevention, Baig and Ali (2006), looked to determine the efficacy of BSE as an early and cost-effective screening measure and discuss the relation of health workers to the education of females in low-income countries. They found that the effectiveness of breast self-exams would come down to the compliance of the individual and that education of risk factors would need to be addressed when educating women about

BSE. Greenwald et al (1978) performed a study that included 293 women and looked at how their breast cancer was detected. About 37% of the women were able to detect their stage 1 tumor through BSE. From this study, it was estimated that breast cancer mortality could be lowered by 18% through BSE. Another study sought to determine the benefit of BSE in relation to the stage at which breast cancer was diagnosed at. Feldman et al. (1981) performed this study and compared the frequency of BSE performed to the stage of the disease at diagnosis. It was found that the greatest difference was between those who practiced BSE monthly and those who rarely or never performed a breast self-exam. 48% of women accounted for those who practiced BSE several times a year that had pathological invasive disease, or stage II breast cancer, were diagnosed before nodal involvement compared to the 38% who rarely performed BSE and the 33% who never performed a breast self-exam. Those who were diagnosed with distant metastasis, stage IV, saw the opposite happen. Those who practiced BSE monthly were only among 2.7% of the women compared to the 14.6% of the women who never practiced BSE. Approximately 84% of the patients who were diagnosed with stage IV breast cancer either rarely or never practiced breast self-exam. This is compared to less than 57% of women who were diagnosed at earlier stages. Along with the stage of cancer, the size of the tumor also varied among those who performed BSE on a monthly basis compared to those who never practiced the self-screening method. The average maximum tumor size for those practicing BSE was 2.5cm, while those who never practiced BSE averaged a tumor size around 3.3cm. The four-year survival rate was also determined to be 73% of the 196 women who practiced BSE monthly and 60% of the 622 women who never practiced. Based on this study it could be determined that performing breast self-exams monthly could benefit women in being diagnosed with an earlier stage of breast cancer, a smaller tumor, and having a greater survival rate after the disease.

While the studies above were able to show benefits to self-breast exams, there are a multitude of studies from the USPSTF, Weiss (2003), and Mayo Clinic that did not have significant enough data to recommend breast self-exams as an efficient screening method. More research should be done to see if there is a present-day association between breast self-exams and tumor size, stage of disease at diagnosis, and mortality. While it may not be recommended as a primary screening method, according to Mayo Clinic$_1$ (2023) it is still recommended that women are aware of their breasts. Breast self-exams could be used as a supplemental tool in order for women to gain more awareness of their breasts in between primary screening methods.

4.4 Breast MRI

4.4.1 How Breast MRI is Performed

According to the American Cancer Society, Breast magnetic resonance imaging (MRI) uses radio waves and strong magnets to make detailed pictures of the inside of the breast. Sometimes a contrast solution, or dye, is used in order to see potentially cancerous tissue more clearly (Mayo Clinic$_2$, 2023). Mayo Clinic details the process of getting a Breast MRI. One will lie face down and place breasts into a cushioned opening. Each opening is surrounded by a breast coil, which detects magnetic signals from the MRI machine. The platform then slides into the MRI machine and the whole imaging process takes about 30 minutes to one hour.

4.4.2 When to Get a Breast MRI

There are a multitude of reasons to have a Breast MRI performed. This section will look at the reasons in relation to breast cancer. Mayo Clinic (2023) suggests that Breast MRIs should be performed: when breast cancer has been diagnosed in order to determine the extent of the cancer, if someone is at high risk of breast cancer, which is defined as a lifetime risk of 20% or greater, if someone has a strong family history of breast or ovarian cancer, if someone has dense breast tissue and a mammogram did not detect a prior breast cancer, if someone has the hereditary breast cancer gene, such as BRCA1 and BRCA2. Mayo Clinic also points out that Breast MRI is intended to be used along with mammography.

4.4.3 Benefits and Harms of Breast MRI

Because MRIs use magnets and do not use x-rays, a benefit to Breast MRI is that it does not expose the patient to radiation (Mayo Clinic$_2$, 2023).

Potential harm to Breast MRIs is the potential for a false-positive result. The MRI may identify a suspicious area that needs further evaluation and if it turns out to be benign, then the detection of the suspicious area would be classified as a false-positive. False-positives can cause unneeded anxiety and additional testing. Another potential harm to MRI is, if a contrast solution is being used to make the images clearer, there is a potential for there to be an allergic reaction to the dye. This allergic reaction to contrast solution can cause serious problems for people with kidney issues (Mayo Clinic$_2$, 2023).

While Mayo Clinic and other institutions are able to lay out specific benefits and harms, the USPSTF concludes that there is insufficient evidence to assess the balance of benefits and harms for supplementary screening, which is the category that breast MRI falls into. The overall grade Breast MRI received was an “I” (USPSTF, 2016).

4.5 Ultrasound

4.5.1 How Breast Ultrasound is Performed

A breast ultrasound uses sound waves and their echoes to make computer images of the inside of the breast. Ultrasound is able to show breast changes that may have been harder to see on a mammogram, like fluid-filled cysts. It is done by putting gel on the skin or a handheld wand, which is the transducer. The transducer out sound waves that can pick up echoes as those waves bounce off of body tissues under the skin. The echoes are then made into an image on a computer screen (American Cancer Society [2], 2023).

4.5.2 When to Get a Breast Ultrasound

The American Cancer Society[2] (2023) suggests that breast ultrasound is useful for looking at some breast changes, because it can differentiate between fluid-filled cysts and solid masses. It can also be helpful in women with dense breast tissue, because a mammogram cannot differentiate between dense breast tissue and potential masses.

4.5.3 Benefits and Harms of Breast Ultrasound

When a breast ultrasound is used supplementally to mammography, it is able to detect occult breast cancers. A study performed by Nothachker et al. (2009) found that supplemental breast ultrasound was able to diagnose invasive breast cancer in 0.32% of women with dense breast tissue after a negative mammogram. While breast ultrasound was able to detect cancer when mammography could not, this number was incredibly small and this study found adverse effects as well. It found that three times more women would need to undergo biopsy per carcinoma detected by ultrasound compared to cancers that are detected by mammography screening alone.

One study found that breast ultrasound was more sensitive than mammography. For women with non-fatty breasts, mammography found 78% of all cancers in women, while ultrasound found 89%. For women with dense breasts, mammography found 57% of cancers, while the ultrasound was able to see 79% of cancers. When ultrasound was used as a supplemental tool and combined with mammography, 96% of cancers were detected. Ultrasound was able to detect small, less than 1 cm invasive cancer better in dense breasts (Berg, 2003).

Another study found that there is not enough evidence to suggest that ultrasound is effective as a supplemental tool to mammography for women of average risk of breast cancer. For women of high risk, there was only low-quality evidence that ultrasound as a supplemental tool could erect additional cases of breast cancer. There was also an increase in false-positive results and subsequent biopsy recommendations for these false-positive findings (Health Quality Ontario, 2016). The USPSTF (2016) also concluded that there was insufficient evidence to support the use of ultrasound and that the potential benefits do not outweigh the potential harms (false-positive results), giving it a Grade I.

CHAPTER 5

SCREENING METHODS IN REALTION TO RISK FACTORS

There is a difference between average risk and high risk of breast cancer in women. Based on what category of risk a woman falls into, can dictate what screening method would be recommended. Average risk is defined as women with no previous breast cancer, no history of breast cancer in a first degree relative, no known mutations in the BRCA1/2 genes, and no previous exposure if the chest wall to radiation (The Canadian Task Force on Preventive Health Care, 2011). The ACS recommends that a woman with an average risk of breast cancer should undergo mammography regularly starting at the age of 45 (Oeffinger et al., 2015). However, starting within this age range only has a Grade C from the USPSTF and is only recommended as an individual decision. The grade for mammography only increases to a B for those 5 years older (USPSTF, 2016). The American Cancer Society and United States Preventive Services Task Force puts out contradicting recommendations for those of average risk.

A woman is considered to be at high risk for breast cancer if they have a 1.67% chance of developing breast cancer in the next five years, or a lifetime risk of at least 20% (McGuinness, 2021). This means that women with multiple factors that increase the chance of them developing breast cancer would place them in the high-risk category. For women that are at high risk of developing breast cancer, many studies compare mammography alone to mammography plus a supplemental screening method. Lehman et al. (2005) performed a study where out of 367 women, who completed all study examinations, 38 biopsies were recommended and 27 biopsies were performed. From those biopsies, 4 cancers were diagnosed, giving a 1.1% cancer yield. MRI was able to detect all 4 of the cancer, where mammography was only able to detect one. The diagnostic yield for mammography was 0.3% and the yield for MRI was 0.8%. MRI was able to detect occult breast cancer in high risk women that mammography was not.

Another study by Lord et al. (2007) compared mammography alone to mammography with MRI and to mammography, MRI, and ultrasound. Evidence showed that adding MRI provided a highly sensitive screening strategy. The table below depicts the screening methods along with their sensitivity ranges.

Table 10: This table configures the sensitivity range for different breast cancer screening methods (Lord et al., 2007).

Screening Method	Sensitivity Range
MRI	93-100%
Mammography	25-59%
Mammography + Ultrasound	49-67%
MRI + Mammography	94%
MRI + Mammography + Ultrasound	44%

Overall, this data shows that mammography with MRI was more sensitive than mammography alone. However, this study also pointed out that adding MRI made it 3-5 times more likely that patients would be recalled for false-positive results.

The USPSTF has supplemental screening, like BSE, MRI and ultrasound, at a Grade I due to not knowing the net benefits and harms. More evidence is needed on the benefits and harms of MRI and Ultrasound in order to recommend them as supplemental screenings. As of now there are many contradicting recommendations that need to be made consistent and should take into account a woman's risk factors.

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