INTRODUCTION
Breast cancer is the second most common cause of cancer in women and the second most common cause of death (1). Mammography screening for breast cancer can reduce the rate of death from breast cancer in women who are 40 years of age or older. However, film mammography has limited sensitivity for the detection of breast cancer in women with radiographically dense breasts and the film contrast cannot be altered or adjusted for subtle differences in tissue. Digital mammography was developed to overcome some of the limitations of traditional film mammography but it also has its disadvantages. Digital mammography systems are costly and currently cost 1.5 to 4 times more than film systems. Do the advantages of digital mammography justify the increased cost? The purpose of this paper is to evaluate the sensitivity and specificity of digital versus film mammography in screening for breast cancer in asymptomatic patients.

BACKGROUND
Breast cancer is a malignant proliferation of the epithelial cells that line either the ducts or lobules of breast tissue. It can arise from epithelium that lines large or intermediate sized ducts (ductal) or from epithelium of the terminal ducts of the lobules (lobular). In general, breast cancer growth can be invasive or in situ. Most breast cancers arise from intermediate ducts (ductal) and are invasive (invasive ductal or infiltrating ductal) (2). Breast cancers can be categorized further into, noninvasive intraductal, infiltrating ductal (which can consist of medullary, colloid, tubular, or papillary), invasive lobular, lobular in situ, and rare cancers such as juvenile, adenoid cystic, epidermoid, or sudoriferous (2).

Breast cancer is the second most common cancer among women second to skin cancer (1). There were approximately 180,510 cases of invasive breast cancer with about 40,910 deaths in the United States during 2007 (1). Over the last 60 years, the incidence of breast cancer has more than doubled from 55 per 100,000 persons to 118 per 100,000 persons in 1998 (3). The occurrence peaked in 1998 and has decreased 9.8% since (3). Women in the age range of 50-69 years of age saw an even larger decrease of 12% (3). This may be due to improved nutrition and reduction in hormone replacement therapy.

There are many factors associated with an increased risk of breast cancer. Breast cancer is 3-4 times more likely to develop in those patients whom have had a sister or mother with breast cancer (2). Furthermore, the risk is increased in patients’ whose mothers’ or sisters’ breast cancer occurred before menopause, were bilateral, in those with a family history of breast cancer in two or more first degree relatives, and in women of Ashkenazi Jewish decent (2). Nulliparous women and women who had their first pregnancy after the age 35 have a 1.5 times higher incidence of breast cancer than multiparous women (2). Previous cancer in one breast will increase the incidence of cancer in the contralateral breast and will increase at a rate of 1-2 percent per year (2). Early onset of menarche (< 12 years) or late natural menopause (> 50 years) is associated with a slight increase risk of breast cancer (2). Women with cancer of the uterine corpus have a significantly higher risk than the general population and also women with endometrial cancer have a comparable risk (2). Concomitant administration of progesterone and estrogen may markedly increase the incidence of breast cancer than estrogen alone (2). Fibrocystic conditions, when present with proliferative changes, papillomatosis, or atypical epithelial hyperplasia, also increases the incidence of breast cancer (2). The consumption alcohol can also slightly increase the risk.

Genetic factors such as inheritance of BRCA1 or BRCA2 gene can increase the risk of breast cancer significantly. The BRCA1 gene is found on chromosome 17 and is mutated in...
early onset breast cancer. The BRCA1 gene mutation will increase a woman’s family with a chance of developing breast cancer to 85% over their lifetime (2). Other genes that are associated with an increased risk of breast cancer and other cancers include BRCA2 (on chromosome 13), ataxiatelangiectasia mutation, and mutation of the tumor suppressor gene p53. Mutations of the p53 gene are associated with about 1% of breast cancers in women under the age of 40 years old (2). Women with an exceptional family history of breast cancer should be counseled and given the option to have genetic testing.

Clinically breast cancer presents with 70% of patients complaining of a painless lump in their breast and about 90% of breast masses are discovered by the patient themselves (2). Other symptoms that may occur but are less frequent are breast pain, nipple discharge, erosion, retraction, enlargement, redness, itching of the nipple, generalized hardness, enlargement, or shrinkage of the breast (2). Important signs that are more indicative of malignant disease are slight skin or nipple retraction or asymmetry of the breast. Breast cancer usually presents as a nontender, firm or hard mass with margins that are poorly defined. Paget’s carcinoma may manifest as very small (1-2mm) erosions of the nipple epithelium. If metastatic disease is present, the patient may present with weight loss, jaundice, back or bone pain. Anatomically, 60% of carcinomas are located in the region of the right upper quadrant (2). Metastases may involve lymph nodes which typically present larger than 1cm and are firm or hard. Advanced metastatic disease is marked by axillary nodes that are matted or fixed to skin or deep structures. Also, masses present in the axillary region may result in swelling of the ipsilateral arm due to infiltration of regional lymphatic vessels.

Differential diagnosis for breast cancer should include the following lesions in descending frequency: fibrocystic condition of the breast, fibroadenoma, intraductal papilloma, lipoma, and fat necrosis.

The primary purpose of screening mammography is to detect small breast cancers. When using film mammography, it is harder to detect breast cancer in younger women or women with dense breast tissue because their normal breast tissue is the density of carcinoma. Therefore, it is difficult to differentiate between the two. As women age the breast tissues atrophy and tumors are more easily visualized on film mammogram. Digital mammography was developed to overcome these issues. One of the advantages is that the contrast of the image can be altered. This may allow for subtle differences in tissue to be detected.

Mammogram screening is an effective means of detecting early breast cancer in the asymptomatic stages and improving survival. Annual screening after the age of 50 can reduce the chance of dying from breast cancer 25 to 30% and the data for women in their 40’s is almost as positive (1).

For early cancer screening and prevention the American Cancer Society recommends yearly mammograms starting at the age 50, clinical breast exams every 3 years for women in their 20’s and 30’s, and yearly mammograms for women in their 40’s (4). Women with a greater than 20% lifetime risk should get an MRI and a mammogram every year (4). Women with 15% to 20% lifetime risk should consult their health care provider about the benefits and limitations of adding an MRI to their yearly mammogram (4). Breast self exams for women starting in their 20’s will allow women to know their breasts and report any changes.

Ultrasonography can be used to differentiate cystic lesions from solid lesions. In addition, it may reveal characteristics highly suggestive of malignancy such as irregular margins. It can also be used to guide a needle to aspirate the fluid and make the diagnosis of a cyst.

Other imaging modalities such as, ductography can be useful to identify the site of an intraductal lesion causing bloody nipple discharge. MRI is highly sensitive but not specific and should not be used as a screening tool (2). However, it may be helpful in examining for multicentricity of a known primary cancer, examining the contralateral breast in women with cancer, and determining the response to neoadjuvant chemotherapy. A PET scan may be useful in examining regional lymphatic and distant disease but not in the evaluation of the breast tissue.

Definitive diagnosis of breast cancer is made by examining tissues or cells removed by biopsy. Suspicious lesions found on physical exam or demonstrated by mammography should be biopsied. Clinically, 30% of lesions believed to be benign are found to be malignant (2). The simplest method of biopsy is either fine-needle aspiration or core needle biopsy. Fine-needle aspiration is a technique where cells are aspirated with a small needle and examined cytologically. The disadvantages are that it requires a skilled pathologist. In addition, deep lesions can be missed and invasive cancers usually cannot be distinguished from noninvasive cancers.
with this technique. The incidence of a false-positive result is extremely low; about 1-2% (2). The false-negative rate can be as high as 10% (2). Core biopsy removes a core of tissue with a large cutting needle under local anesthesia. The main issue is sample collection error due to improper positioning of the needle yielding false-negative results (2). Open biopsy consists of either an incisional biopsy or excisional biopsy and is used after a non-diagnostic needle biopsy. Both procedures take place with the patient under general anesthesia. During an incisional biopsy, only a portion of the abnormal tissue is removed where as with an excisional biopsy, an attempt is made to remove the entire abnormality. Typically, the outpatient open biopsy is followed by a definitive operation at a later date to allow the patient to adjust to the diagnosis of cancer, consider alternative therapy and allow for the patient to seek a second opinion if they wish. Computerized stereotactic guided core needle biopsy is recommended when a suspicious abnormality is identified by mammography alone and clinically cannot be palpated by the clinician. In this case, the biopsy needle is inserted into the lesion under mammographic guidance and a several core tissue samples are removed for histological examination.

Laboratory findings may include an elevated sedimentation rate which may be the result of disseminated cancer and elevated serum alkaline phosphatase may be the result of liver or bone metastases. Other markers such as carcinoembryonic antigen (CEA) and CA 15-3 or CA 27-29 can be used to monitor for recurrent breast cancer, but are not useful in the diagnosis early breast cancer.

The presence of estrogen receptors (ER) or progesterone receptors (PR) in the tumor cells is of major importance in how the patient is managed. Patients with primary tumors that are receptor positive have a more favorable outcome (2). Up to 60% of patients with ER-positive tumors will respond to adjuvant hormonal therapy and up to 80% of patients with PR-positive tumors will respond to hormonal manipulation (2). Receptor status has no relationship response to chemotherapy (2). The ER, PR, proliferative indices, and Her-2/neu status should be determined at the time of the initial biopsy. The proliferative indices are important because they establish the rate of growth and differentiation of the tumor and the Her-2/neu status will help determine the prognosis and recurrence rate (2).

A uniform breast cancer staging system, TNM (primary tumor, regional lymph nodes, metastases), has been established and agreed upon by the American Joint Committee on Cancer and the International Union Against Cancer (2). The TNM system allows for a universal means of communication between investigators and clinicians (2). It also allows for therapeutic decision making and accurate prognosis. The size of the tumor is designated by (T) and can range from T0 to T4. The extent of regional lymph node infiltration is designated by (N) and can range from N0-N3. The presence of distant metastasis is designated by (M) and is ether M0-M1. The letters TNM in combination with numbers determine the staging of cancer present. The stage of cancer can range from stage 0 to stage 4.

Treatment for breast cancer may be classified as either curative or palliative. Curative treatment can be used for clinical stages 1, 2, and 3 of disease. The standard of care for stage 1, 2, and most of stage 3 is surgical resection. Studies show that disease free survival rates are similar for patients treated with partial mastectomy plus axillary dissection followed by radiation therapy and those treated modified radical mastectomy (2).

Adjuvant systemic therapy is recommended for patients with curable breast cancer following surgery and radiation therapy to eliminate occult metastases. Adjuvant systemic therapy consists of chemotherapy or hormonal therapy. Chemotherapy has been proven to increase survival for node positive and node negative disease and in pre- or postmenopausal women (2). The standard of care is cyclophosphamide, methotrexate, and fluorouracil (CMF) given on days 1 and 8 of each month for 12 months (2). Other studies show that adriamycin and cyclophosphamide (AC) and epirubicin and cyclophosphamide (EC) are at least as effective as CMF in node negative women (2). Adjuvant hormonal therapy is highly effective in decreasing mortality and recurrence in women with estrogen receptor (ER) positive tumors (2). The standard regiment for adjuvant hormonal therapy is tamoxifen for 5 years.

Palliative therapy is indicated for disease that is incurable by surgery (stage 4) and patients whom have had previous treatment and developed distant metastases or unresectable local cancer. Palliative radiotherapy can be used for locally advanced cancers to control ulceration, pain and other manifestations that may occur and palliative hormone manipulation may be helpful in pre- or postmenopausal women as well. Tamoxifen is the most commonly used therapeutic agent for hormonal manipulation (2). Palliative chemotherapy should be considered if there are visceral metastases present, if the hormonal treatment is unsuccessful or the disease has progressed after initial response to
hormonal therapy, or if the tumor is ER-negative (2). The most effective single agent used is doxorubicin (Adriamycin) (2).

Mortality rates of breast cancer became stable during the latter half of the 20th century making breast cancer second to lung cancer mortality rates (3). During the 1990’s, mortality rates declined even more at an average of 2.1% annually (3). Furthermore, in 2003, the mortality rate was the lowest level since 1969 when national statistics began to be kept (3). The reduction in mortality can be attributed to adjuvant therapy but 28 to 65% is most likely due to mammogram screening (3).

METHODS
This paper asks the question, “Is film or digital mammography more sensitive and specific for detecting breast cancer?” this question addresses diagnosis/screening and is best supported through evidence obtained in a prospective, blind comparison to gold standard study which is evidence level 1/A . A computerized literature search for relevant studies was performed in Google Scholar to isolate recent studies. The following text words were used during the search; digital vs. film mammography, breast cancer, mammography screening and women screening. The search was restricted to English language and full text articles only. The search was limited to articles published later than 2005 to access more current information. The articles “Diagnostic Performance of Digital versus Film Mammography for Breast-Cancer Screening” and “Full-Field Digital Versus Screen Film Mammography: Comparative Accuracy in Concurrent Screening Cohorts” were then distracted from their original databases, The New England Journal of Medicine and American Journal of Roentgenology, respectively.

DISCUSSION
The article Diagnostic Performance of Digital versus Film Mammography for Breast-Cancer Screening also known as the Digital Mammographic Imaging Study Trial (DMIST) was designed to measure relatively small but potentially clinically important differences in diagnostic accuracy between digital and film mammography (5). The study was conducted by Pisano et al, funded by the National Cancer Institute and took place over a two year period.

The study initially recruited 49,528 women that were evaluated at 33 different sites. Women who presented for screening mammography were eligible to participate unless they reported symptoms, had breast implants, believed they might be pregnant, had undergone mammography for any reason within the preceding 11 months, or had a history of breast cancer treated with both lumpectomy and radiation.

All women who participated in the study underwent both digital and film mammography in random order. There were 5 different digital mammography systems used in this study. The digital and film examinations for each individual were interpreted by two radiologists; one reader for each examination. To estimate the sensitivity, specificity and positive predictive values, the reader rated the films on a 7 point malignancy scale, the Breast Imaging Reporting and Data System (BIRADS) scale and the presence or absence of workup recommendation by the radiologist. The seven point malignancy scale was dichotomized as negative (score of 1, 2 or 3) or positive (score of 4, 5, 6 or 7) and was suitable for receiver operating characteristic (ROC) analysis and the classification according (BIRADS) scale. The readers also rated breast density according to the standard BIRADS scale.

A diagnostic work-up, which included biopsy or aspiration, was performed on any lesions that appeared suspicious. All pathological diagnoses were coded by a principal investigator of the study based on cytological, histological or local pathology report. All participants, with or without pathological diagnosis were asked to return for a follow up film and digital mammograms in one year with. Participants were considered positive for breast cancer if the cancer was pathologically verified within 455 days from the initial mammogram. Participants were considered negative for cancer if the pathology report of their biopsy specimen was negative, if the follow up mammogram at 1 year was normal, or if both criteria were met. Participants were considered indeterminate if they had a breast biopsy with indeterminate results, had a follow up mammogram with a BIRADS score of 3, 4, or 5, or died during the follow up period without receiving a diagnosis of breast cancer.

Out of the 49,528 women enrolled in the study, 195 were subsequently determined to be ineligible, 194 withdrew from the study, and 1489 were excluded from analysis because the study protocol had not been followed at one participating institution. Thirty nine women were excluded because the same radiologist interpreted both examinations or the radiologist knew the result of the other examination at the time of interpretation and 12 were excluded because the examinations were technically inadequate. Follow up information was lacking for 4339 and 500 had an
indeterminate cancer status which left data for a total for 42,760 women for primary analysis.

The demographics of the women enrolled in the study were similar as listed as: mean age 54.9 years, white 84.4%, Hispanic or Latina 3.0%, Black or African American 9.9%, Native Hawaiian or other Pacific Islander 0.1%, Asian 1.9%, American Indian or Alaskan Native 0.1%, other race specified 0.6%, and unknown or data missing for ethnicity 0.1%. The menopausal status was listed as: premenopausal 28.1%, perimenopausal 8.8%, postmenopausal 61.0%, unknown or missing data for menopausal status 2.0%. The breast density was classified as: almost entirely fat tissue 10.2%, scattered fibroglandular densities 43.2%, heterogeneously dense 39.3%, extremely dense 7.3%, and data missing for breast density (<0.1%).

The results showed that the diagnostic accuracy of digital and film mammography was similar and there was no significant difference between the two overall. There was also no significant difference between digital and film mammography according to race, the risk of breast cancer or type of digital machine used. The performance of digital mammography was significantly better among women under the age of 50, women classified by the readers as having heterogeneously dense or extremely dense breasts, and in premenopausal or perimenopausal women.

In critiquing this study, I felt it was well written and performed. The authors clearly explained the purpose of the study. They used a large sample size which makes the study more accurate for the general population. They explained the methods section clearly, particularly what they were measuring and how they were analyzing the data. They clearly defined the exclusion criteria for the study and the reasoning for it. All the participants including those that were excluded from the study were accounted for. The results were thorough and explained well.

All women who reported to one of the study sites were eligible for the study. The demographics and characteristics were similar in the women who were enrolled in the study and the women who were excluded from the study negating any exclusion bias in age, race, ethnicity, menopausal status or breast density. All women enrolled in the study underwent both film and digital mammography so there is no evidence of selection bias. The demographics of the women enrolled in the study were similar to that of the general population. Therefore, the results would be applicable to the general population.

The article “Full-Field Digital Versus Screen Film Mammography: Comparative Accuracy in Concurrent Screening Cohorts” was a study conducted from January 2004 to October 2005 in Florence, Italy to compare the diagnostic accuracy of digital mammography versus film mammography (6). The study evaluated patients that were part of a breast cancer screening program that has been present since 2001. The screening program has several mobile units that are placed around Florence, Italy and are equipped to with either digital or film mammography. The investigators compared two mobile units, one digital and one film, that had similar cancer detection rates. They evaluated screening mammograms obtained from January 2004 to 2005 from the two mobile units.

The study initially obtained 14,706 digital mammograms and 21,556 film mammograms. The mammograms were compared and matched by decade of life and reviewing radiologist leaving two groups of 14,385 participants each which were included in the study. Each group underwent either film or digital mammography.

Screening was offered to all women ages 50-69 years old. Since each group was matched by decade of life both groups had 46.9% women 50-69 years old and 53.0% 60-69 years old. There were 135 subjects who were initially excluded before matching by age and reviewing radiologist because they underwent mammography for assessment of symptoms.

The digital and film mammograms were interpreted by four radiologists. During the time of imaging there was no real time feedback provided for film mammography, but feedback was available for digital mammography because the image was obtained instantaneously on the monitor. Double review of the mammograms was performed with the second reviewer aware of the first reviewer’s report. Recall of the patient for further assessment was based on suspicion by either viewer. Computer assisted detection was not used for digital or film mammograms since it was not standard practice at that time.

The data recorded for each participant consisted of age group (50-59 years or 60-69 years), screening round (first or second), reviewing radiologist, mammographic density categorized as percentage volume occupied by fibroglandular density, screening test outcome, reason for recall, type of radiologic abnormality prompting recall, and final outcome of diagnostic outcome. The researchers compared the accuracy of digital mammography versus film mammography for recall, cancer detection rate, positive
predictive values at recall in the overall series and according to variables such as age, breast density, prevalence or incidence, screening round, and type of radiologic abnormalities. They extended the evaluation by reviewing all participants recalled on the basis of the presence of microcalcifications.

Overall, 14,385 mammograms were obtained with each technique. The statistical significance for the data was set at \( p < 0.05 \). The results showed that digital mammography was associated with significantly more recalls than film mammography because of radiologic abnormality. In addition, digital mammogram had significantly less recall due to poor technical quality. Digital mammography had a significantly higher recall rate because of a higher rate of detection of calcifications than did film mammography, but the recall rates did not differ for masses or distortions. For women in the age range of 50-59 years old, the recall rate for radiologic abnormality was significantly higher for digital mammography than for film mammography. Recall rates were significantly higher for digital mammography than film mammography for women with very dense breast which the authors attribute to greater radiologic uncertainty.

There were 188 cancers detected; 84 by film mammography and 104 by digital mammography. Out of the 188 detected, there were 144 invasive cancers (69 in film mammography and 75 in digital mammography) and 44 were ductal carcinoma in situ (DCIS) (15 in film mammography and 29 in digital mammography). The frequency of detection of early stage lesions was higher in digital than film mammography \((p=0.06)\).

Significantly more cases of cancer depicted as microcalcifications were detected on digital mammography than on film mammography which caused the recall rate and cancer detection rate to be higher.

This study compared two large cohorts of participants from a single population. The groups of participants had similar composition as to age, breast density and screening round. The main difference between the two groups was the screening modality received (digital or film mammography).

The study showed more cases of cancer were detected with digital than with film mammography. The higher detection rate was more evident among younger women and women with denser breasts, but was not statistically significant. Digital mammography had a higher recall rate and a higher cancer detection rate, but the difference was not statistically significant. Digital mammography was associated with less need for recall because of poor technical quality than film mammography, but digital mammography had the advantage with real-time processing.

In critiquing this study, I felt it was fairly well written. The purpose of the study was clearly stated in the introduction. The methods were a little confusing as to what sample of the population was receiving which treatment and how they matched the cohorts for comparison which left the reader guessing or assuming. The digital screening mobile unit had an advantage because real time feedback was available on the monitor whereas with the film mammogram mobile unit, this luxury was not available. This issue is important because the screening was performed in mobile units and quick film processing was not available to check for poor quality of the films. Therefore, film mammography would be expected to have a higher recall rate for poor quality. Another problem with this study is that the mammograms were viewed twice with the second radiologist being aware of the first radiologists’ report. This could cause bias since the second reader may be more likely to agree than disagree with initial radiologist’s report. The authors extended the study by reviewing participants recall on the basis of the presence of microcalcifications. This may be problematic since they were not prepared to evaluate this data. If anything, this may provide a basis for future studies.

All of the participants in the study were accounted for. One of the possible limitations of this study is that they compare one screening method relative to another.

This type of cohort study is not the best way to evaluate and compare the detection rate of the two screening procedures. Each group was only receiving only one treatment either digital or film mammography. Therefore, it is not known if either imaging study would have detected the false negatives of the other screening procedure. To better compare the two screening procedures, a blind comparison to the gold standard would have been the best type of study to test this hypothesis.

CONCLUSION

Pisano et al (5) showed that digital mammography was significantly better than traditional film mammography at detecting breast cancer in young women, premenopausal, perimenopausal women, and women with dense breast tissue. They also found that there was no significant difference in diagnostic accuracy between digital and film mammography in the population as a whole or in other
predefined subgroups defined by race, risk of breast cancer, type of digital machine used, women 50 years of age or older, women with fatty breasts scattered fibroglandular densities, and postmenopausal women.

Rosselli et al (6) showed that digital mammography was associated with significantly more recalls than film mammography because of radiologic abnormalities and with significantly less recall than film mammography because of poor technical quality. Digital mammography also had a significantly higher recall rate because of its better capability to detect calcifications than film mammography. In women age 50-59 years old, the recall rate was significantly higher for digital mammography than it was for film mammography. In addition, significantly more cases of cancer were detected as microcalcifications on digital mammography than on film mammography.

Both studies showed that digital mammography is either as sensitive and specific or more sensitive and specific than film mammography. Therefore, digital mammography leads to additional cancer detection in the population. Digital mammography has advantages over film mammography in that the operator has the option to access the images immediately for quality assurance. It also has improved means of transmission, picture retrieval, storage of images, and the use of a lower dose of radiation without compromising diagnostic accuracy. In addition, the digital images can be enhanced and manipulated to allow visualization in subtle changes in tissue structure throughout the entire breast. More studies are needed in the future to evaluate the cost effectiveness of digital mammography and the associated equipment needed to view the digital mammograms.

References
Author Information

Larry Arnold, PA-S
King’s College Department of PA Studies St. Wilkes Barre, Pennsylvania