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Review Article

Carcinoma breast in pregnancy and lactation

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ABSTRACT

Breast carcinoma is the most common malignancy associated with pregnancy. The incidence is low but increasing due to increasing number of late pregnancies. Symptoms and signs of the disease may be overlooked, resulting in delays in treatment and potentially compromising survival. For this reason, it is imperative that physicians perform careful clinical breast examinations in all pregnant patients—particularly early in gestation, before the breasts become difficult to examine. Upon finding any suspicious breast mass, an open biopsy without delay is indicated. Modified radical mastectomy may be safely performed and is the primary treatment of choice when cancer is diagnosed during pregnancy. Chemotherapy can be given in late pregnancy, and radiotherapy is best avoided. In some cases, especially when disease presents early in gestation, an interruption of the pregnancy may be warranted. Importantly, stage for stage, breast cancer during pregnancy has a similar prognosis to that of breast cancer in young, nonpregnant women; pregnancy itself does not appear to have an adverse effect on the disease process. There is no need for therapeutic abortion. Stage by stage, the prognosis of breast carcinoma in pregnancy is similar to that of non-pregnant controls. With careful counseling, further pregnancy can be planned after 2-3 years in selected cases.

KEY WORDS

Carcinoma, breast, cancer, malignanacy, pregnancy, lactation

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INTRODUCTION

The most frequent malignancy concurrent with pregnancy is breast cancer.[1-5] Pregnancy associated breast carcinoma (PABC) is defined as that being diagnosed during pregnancy, or within one year thereafter.[6,7] Approximately 2-3% of all breast cancers coincide with pregnancy or lactation and this tumour affects only one to four out of 10,000 pregnant women, and is thus a rare occurence.[8,9,10] Therefore, most family practitioners, surgeons and obstetricians encounter a pregnant woman with breast cancer only once every several years. Partly because of the rarity of this clinical entity, misconceptions about the natural history and prognosis of this disease have persisted. These misconceptions have adversely affected both the timeliness of diagnosis and the appropriateness of treatment in a pregnant woman who presents with a breast mass.[5] It appears that pregnancy and breast cancer are merely coincidental and that pregnancy or lactation does not directly contribute to the development or accelerated progression of breast cancer.[11,12] The most common presentation of a malignant tumor is a painless lump, usually discovered by the patient.[13]

Breast cancer during pregnancy involves a host of psychosocial, ethical, religious, and legal considerations; and historically has placed the welfare of the mother in conflict with that of the fetus. Although the diagnosis of breast cancer during pregnancy may be only a biological coincidence, the emotional impact of this coincidence can be devastating on both patient and family. Informed medical care and compassionate support are both essential for women who simultaneously must confront the diametrically opposed implications and expectations of a life-giving and a life-threatening process. Other special

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considerations with pregnancy-associated breast cancer include the timing of delivery, the potential for nursing, and concerns for future fertility.

DELAYED DIAGNOSIS

Multiple studies have documented a delay in diagnosis in breast cancer during pregnancy.[14-25] Generally, 40% to 50% of nonpregnant young women with breast cancer present with disease metastatic to axillary lymph nodes.[26] In contrast, several recent studies have documented lymph node metastasis in 56% to 89% of pregnant women with breast cancer.[14,17,18,27-29] Since breast cancer during pregnancy is not inherently a different disease from breast cancer in a young patient, the advanced stage of disease at presentation is more likely secondary to delay in diagnosis. There is an average reported delay of 5 to 15 months from the onset of symptoms.[12,30,31]

Physiologic changes during pregnancy modify the architecture of the breast considerably, and this may account for a significant portion of diagnostic delay. Due to the normal increase in secretion and release of ovarian placental estrogen and progestin during pregnancy, the breast enlarges, the ducts and lobules proliferate, and the breast prepares for active secretion[32-34]These changes dramatically alter the breast structure, resulting in enlargement, firmness, and increased nodularity. The clinician examining the breast of a pregnant patient may mistake a dominant mass for the normal physiologic alterations of pregnancy. In addition, as the pregnancy progresses, these changes may become more pronounced, potentially obscuring a worrisome mass. As a result of these changes in the breast during pregnancy, delay in diagnosis occurs with disappointing frequency, possibly leading to poorer survival rates in pregnant as compared with nonpregnant women.[32,34]

DIAGNOSTIC TOOLS

To detect breast cancer, pregnant and lactating women should practice regular judicious self-examination. A thorough and careful clinical breast examination of the pregnant females at the initial visit to the obstetrician, before the breasts become enlarged and difficult to examine, is necessary, and should be continued thereafter. When a physician identifies a clinically suspicious, dominant mass-a mass discrete and distinct from surrounding tissue—in a pregnant woman, proper referral and diagnosis are necessary.[5]

There are 2 significant differences in diagnosing breast cancer in pregnant women compared to nonpregnant women. These involve the use of fine needle aspiration cytology (FNAC) and mammography. When a pregnant woman presents with a palpable, dominant breast mass, fine needle aspiration should be performed at the initial visit, as with a woman who is not pregnant. This technique is most useful in differentiating a cyst or galactocele from a solid lesion. If a solid mass is encountered, however, FNAC may be misleading. False-positive results have been reported and are believed to be due to hormonally related cellular atypia during pregnancy.[35] Therefore, it is recommended that open biopsy be performed in a timely manner when a solid mass is identified during pregnancy. USG is a safe and accurate way to differentiate between solid and cystic lesions.[34]

Mammography is widely employed by many physicians to aid in the evaluation of a suspicious breast mass. With proper shielding, mammography poses little risk of radiation exposure to the fetus and the irradiation dose to fetus is minimal (less than 0.50 mrem).[36,37] However, mammograms should only be used to evaluate dominant masses and to locate occult carcinomas in the presence of other suspicious physical findings.[37] A mammogram during pregnancy is not easy to read and has at least 25% false-negative rate because of the increased water content of the breast tissue and the loss of contrasting fatty tissue that usually defines a mass.[34,36,38] In a series by Max and Klamer,[39] mammograms were read as normal in 6 of 8 pregnant women who had palpable breast masses later diagnosed as cancer. Thus, in a pregnant woman with a suspicious breast mass, a mammogram interpreted as normal may mislead the physician into delaying an open biopsy.

In the setting of pregnancy, there simply is no substitute for a properly performed open biopsy. This is particularly true in light of the diagnostic inadequacy of FNAC and mammography during pregnancy. Importantly, there is no evidence to suggest that a breast biopsy poses any significant anesthetic risk to either the fetus or the mother. In a report of 134 breast biopsies performed on pregnant women with general anesthesia, Byrd and coworkers[40] documented only 1 fetal loss. Clearly, breast biopsy during pregnancy is safe and represents the most definitive means of diagnosing a malignancy. To avoid a false-positive diagnosis as a result of misinterpretation of pregnancy-related changes, the pathologist should be advised that

the patient is pregnant.[35,41]

STAGING

Procedures used for staging of breast cancer should be modified to avoid radiation exposure to the fetus in pregnant women. Nuclear scans cause fetal radiation exposure. If such scans are essential for evaluation, hydration and Foley catheter drainage of the bladder can be used to prevent retention of radioactivity. Timing of the exposure to radiation relative to the gestational age of the fetus may be more critical than the actual dose of radiation delivered.[37] Radiation exposure during the first trimester can lead to congenital malformations, especially microcephaly. Doses greater than 100 rad may produce congenital abnormalities in 100% of cases. Doses of 10 rad may result in fewer defects. A chest x-ray delivers 0.008 rad,[42] and bone scan delivers 0.1 rad.[12] Chest x-rays with abdominal shielding are considered safe, but as with all radiologic procedures, they should be used only when essential for making treatment decisions.[12,30] For the diagnosis of bone metastases, a bone scan is preferable to a skeletal series because the bone scan delivers a smaller amount of radiation and is more sensitive. Evaluation of the liver can be performed with ultrasound, and brain metastases can be diagnosed with a magnetic resonance imaging (MRI) scan, both of which avoid fetal radiation exposure. Carcinogenesis in the fetus exposed to radiation is another consideration.

Hormone receptor assays are usually negative in pregnant breast cancer patients, but this may be the result of receptor binding by high serum estrogen levels associated with the pregnancy. However, enzyme immunocytochemical receptor assays are more sensitive than competitive binding assays. A study using binding methods indicated similar receptor positivity between pregnant and nonpregnant women with breast cancer.[43] The study concluded that increased estrogen levels during pregnancy could result in a higher incidence of receptor positivity detected with immunohistochemistry than is detected by radiolabeled ligand binding, due to competitive inhibition by high levels of endogenous estrogen.[43]

TREATMENT OVERVIEW

The management of PABC is very difficult and encompasses many diagnostic and therapeutic dilemmas. The risk to the unborn child plays a major role in the decision process. Ideally the objectives of treatment are to cure the patient of her cancer and deliver a healthy viable infant. Once the appropriate treatment modality is chosen, its implementation must not be delayed because of the pregnancy. The involvement of multiple subspecialties in the management of these patients is highly recommended. The various treatment options are briefly discussed below.

Surgery: Modified radical mastectomy is the mainstay of treatment.[12,30,38,44-46] General anesthesia is safe if the usual precautions are taken to compensate for the physiologic changes induced by pregnancy.[12] Typical anesthetic agents readily reach the fetus but are not known to be teratogenic.[45,47] Since the risk of spontaneous abortion during mastectomy is extraordinarily low, pregnancy is not a contraindication to operative treatment. Modified radical mastectomy is the single treatment modality that allows the pregnancy to continue with minimal risk to both the mother and the fetus. A delay in surgical intervention for breast cancer is as detrimental in a pregnant woman as it is in a nonpregnant woman. Breast conservation therapy, with radiation treatments given after delivery or after neoadjuvant chemotherapy, is an option for women with PABC diagnosed late in pregnancy.[44] Immediate breast reconstruction is not indicated.[13]

Radiotherapy: The standard radiation therapy course consists of whole breast irradiation followed by a boost dose to the tumor bed, for a total of 5000 cGy.[13] The amount of radiation scattered to the fetus depends predominantly on the distance of the fetus from the field center. In the first trimester of pregnancy, the embryo/fetus situated at a maximal distance from field center may be subjected to 10 cGy to 15 cGy of radiation. Toward the end of pregnancy, however, when the top of the uterus approaches the xiphoid, as much as 200 cGy of radiation may be delivered to the fetus.[45] Hence radiotherapy is contraindicated in the first trimester of pregnancy and should be avoided in late pregnancy due to increased internal radiation scatter.[48,49]

It is not known how much radiation can be tolerated by a developing fetus without inducing significant anomalies; precise data are simply not available. Conclusions must be drawn from atomic radiation reports,[50] in which relatively small doses of radiation resulted in significant central nervous system abnormalities. By extrapolation, during the first trimester, when a developing embryo/fetus may receive as much as 10 cGy to 15 cGy of radiation, significant radiation-induced anomalies may arise. Brent, in an extensive review of literature, defined 0.05

Gy as a relatively safe upper limit of fetal exposure.[49]

It is widely believed that any radiation exposure to a developing fetus is not acceptable; therefore, for women with breast cancer diagnosed early in pregnancy, breast conservation therapy should be strongly discouraged. For patients with breast cancer discovered late in pregnancy who insist on breast conservation, it may be reasonable to perform segmental mastectomy with axillary dissection, and delay radiation therapy until after delivery. However, the effectiveness of radiation treatment for preventing local recurrence is unknown in the setting of pregnancy. The breast of a pregnant woman is anatomically and physiologically different from the breast of a nonpregnant premenopausal woman, and these differences may predispose the patient to an increase in local recurrence after breast conservation surgery.[45] Thus, for women who strongly desire breast conservation therapy, there should be an understanding that this treatment may not be equivalent to modified radical mastectomy for purposes of local control.

Chemotherapy: Postoperative chemotherapy is standard treatment for node-positive premenopausal women with breast cancer, and it may also benefit women without nodal metastasis. Although it is not known what length of time is permissible prior to initiating chemotherapy, it is widely believed that delay may ultimately diminish therapeutic benefit.[5,12] Since exposure of the developing fetus to chemotherapeutic agents may result in teratogenesis and other serious complications, the decision to start adjuvant therapy during pregnancy is a difficult one.

Doll DC et al[51] stated that administration of chemotherapy in the first trimester is associated with a high risk (17%) of birth defects, in terms of probability of IUGR, prematurity, fetal malformation, or death; this risk is less (1.3%) in the second and third trimesters. Shapira and Chudley[52] reviewed 71 patients from 8 reports and found a 12.7% rate of fetal malformation during the first trimester. Unfortunately, the exact risks associated with chemotherapy are by no means clear. Anecdotal reports suggest that cytotoxic agents result in teratogenesis, intra-uterine growth retardation, cardiac anomalies, delayed carcinogenesis and other serious side-effects in infants exposed to these chemotherapeutic agents in-utero[12,44,30,53,54,55] These reports showed that the risk of teratogenesis was highest during the first trimester. Neoadjuvant or adjuvant combination chemotherapy consisting of 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) can be given during the second or third trimester with minimal risks to the fetus and minimal complications of labor and delivery; but should usually be delayed until after delivery.[53,54]

The therapeutic decision of whether to initiate chemotherapy depends on the stage of pregnancy and the stage of disease. When a woman is diagnosed with breast cancer during the final trimester of pregnancy, it may be reasonable to delay adjuvant therapy until after delivery. However, because adjuvant therapy may have such deleterious effects on the developing fetus during the first 2 trimesters, and delay in initiating chemotherapy may be harmful to the mother, it may be necessary to consider termination of the pregnancy.[5,12,44] In some cases, this may be the desired option, allowing appropriate therapy without restriction.

Hormonal Therapy: Hormone therapy, such as treatment with tamoxifen, has not been well-studied in pregnant women, either as adjuvant treatment after surgery or as treatment for advanced cancer, so its effects are largely unknown. Tamoxifen should be avoided in the first trimester and possibly beyond.[38] Prophylactic ovarian ablation does not influence significantly the course of PABC and should be undertaken only in case of progressive or recurrent disease.[8]

NEED FOR ABORTION

In the past, when it was thought that pregnancy itself detrimentally stimulated tumor growth, therapeutic abortion was an important element of breast cancer treatment. As it has become apparent that breast cancer during pregnancy is not inherently a different disease from breast cancer in a nonpregnant young woman, enthusiasm for abortion as a therapeutic maneuver has waned. Breast cancer in pregnancy is by itself not an indication for abortion.[6,44,56,57] No damaging effects on the fetus from maternal breast cancer have been demonstrated, and there are no reported cases of maternal-fetal transfer of breast cancer cells.

Whether a woman proceeds with therapeutic abortion depends on the stage of pregnancy, the stage of disease, the desire for breast conservation, and the priorities of the individual patient. In an individual who insists on breast conservation therapy for a cancer discovered during the first trimester, therapeutic abortion may be preferable to exposing the fetus to ionizing radiation.[11,12,13] Similarly, the dangers of

teratogenesis from chemotherapy may convince a woman in her first trimester to terminate the pregnancy, allowing for therapy without hindrance.[11,12,13] There is no evidence that termination of pregnancy improves the outlook for the patients or alter the natural history of breast cancer, but it does permit standard aggressive therapy in advanced disease.[5,12] Hence therapeutic abortion should be performed in all women with advanced-stage disease and in whom a significant delay of this treatment would jeopardize maternal health.[5,11,12]

However, since advanced-stage breast cancer is essentially incurable despite aggressive adjuvant therapy, the well-informed patient may wish to carry the pregnancy to term.[11]

EFFECT OF SUBSEQUENT PREGNANCY ON CARCINOMA BREAST

Breast cancer risk increases with age; therefore, women who delay childbearing gradually move into a higher risk category for the disease. Since many women are delaying childbearing for educational, professional, or personal reasons the number of women who will undergo breast cancer treatment before completing childbearing is increasing[58] The earlier literature stated that at least 7% of women who did not undergo oophorectomy underwent one or more pregnancies, and 70% of these pregnancies were to be expected in the first five years after cancer treatment.[3] Adjuvant cytotoxic chemotherapy depletes the number of fertile patients, but as many as 11% had a deliberate or unplanned pregnancy in a short-term chemotherapy study.[59]

Breast carcinoma is not in itself a contraindication to subsequent pregnancy.[45] Pregnancy does not appear to compromise the survival of women with a prior history of breast cancer, based on limited retrospective data. No damaging effects on the fetus from maternal breast cancer have been demonstrated, and there are no reported cases of maternal-fetal transfer of breast cancer cells.

The available literature shows that breast cancer patients who subsequently become pregnant have good survival rates, often the same or sometimes better than patients with no subsequent pregnancy.[60-72] Kroman et al[68] studied 173 women who became pregnant after treatment of breast cancer; Women who had a full-term pregnancy after breast-cancer treatment had a non-significantly reduced risk of death (relative risk 0.55 [95% CI 0.28-1.06]) compared with women who had had no full-term pregnancy after adjustment for age at diagnosis, stage of disease (tumour size, axillary nodal status, and histological grading), and reproductive history before diagnosis. It has been argued that only women with a good prognosis live to become pregnant, thereby skewing the good results found in pregnancy following breast cancer. The individual woman's prognosis, well-being, desire for children, support from spouse and other socio-economic factors must be carefully considered in this difficult decision-making process.[60]

It is generally recommended that patients wait 2 years after diagnosis before attempting to conceive.[45,53,69] This allows early recurrence to become manifest, which may influence the decision to become a parent. In women with more advanced disease, the prognosis is poor, and the patient should be advised that she may not survive long enough to raise the child of a subsequent pregnancy.[11] Little is known about pregnancy after bone marrow transplantation and high-dose chemotherapy with or without total-body irradiation. Sanders et al studied the data of 1322 patients who had earlier received high dose Cyclophosphamide or total body irradiation (TBI) from 1971-1992 for hematological disorders; and reported 7% and 37% incidence of spontaneous abortion; and 18% and 63% incidence of preterm deliveries, in cyclophosphamide and TBI recipients respectively. The overall incidence of low birth weight infants in this series was 25%, which is higher than the expected incidence of 6.5% for the general population (P = .0001).[63]

Clark and Chua[70] found that 72% of their patients became pregnant within two years of treatment. Those who became pregnant within six months had a comparatively poor prognosis — a 54% five-year survival rate compared to a 78% five-year survival rate among those who waited six months to two years to become pregnant after breast cancer diagnosis. Those who waited five years or more to become pregnant had 100% five-year survival from that point. They concluded that a wait of at least six months from completion of treatment is recommended. The data are consistent with the fact that the longer survival after diagnosis is, per se, an indicator of the patients' better prognosis (whether pregnancy occurs or not). Some pertinent studies on breast carcinoma after pregnancy are summarized as Table 1.

LACTATION DURING CANCER TREATMENT

Suppression of lactation does not improve prognosis.

Table 1: Studies on Breast Cancer after Pregnancy

Author	Year	Number of Patients	Study Period	10-Year Survival Node Negative /Positive
Harvey et al[66]	1981	41	1940-70	80% / 79%
Ribiero et al[18]	1986	57	1941-80	64% / 26%
Mignot et al[71]	1986	68	1940-85	90% / 71%
Ariel and Kempner[72]	1989	46	1950-80	76% / 56%
Clark and Chua[70]	1989	136	1931-85	64%
Sankila et al[73]	1994	91	1967-89	93%
Von Schoultz et al[67]	1995	50	1971-88	*
Kroman et al[68]	1997	173	1978-95	*
Gelber S et al[62]	2001	108	1980-98	86%

*10-year survival not given.

However, if surgery is planned, lactation should be suppressed to decrease the size and vascularity of the breasts also helps reduce the risk of infection in the breast, and can help avoid having breast milk collect in any previous biopsy incisions.

It should also be suppressed if chemotherapy is to be given because many antineoplastics (specifically cyclophosphamide and methotrexate) given systemically may occur in high levels in breast milk and this would affect the nursing baby. In general, women receiving chemotherapy should not breast-feed.[5,12]

CONCLUSION

Breast carcinoma is the most common malignancy associated with pregnancy. The incidence is low but increasing due to increasing number of late pregnancies. Symptoms and signs of the disease may be overlooked, resulting in delays in treatment and potentially compromising survival. For this reason, it is imperative that physicians perform careful clinical breast examinations in all pregnant patients—particularly early in gestation, before the breasts become difficult to examine. Upon finding any suspicious breast mass, an open biopsy without delay is indicated. Modified radical mastectomy may be safely performed and is the primary treatment of choice when cancer is diagnosed during pregnancy. Chemotherapy can be given in late pregnancy, and radiotherapy is best avoided. In some cases, especially when disease presents early in gestation, an interruption of the pregnancy may be warranted. Importantly, stage for stage, breast cancer during pregnancy has a similar prognosis to that of breast cancer in young, nonpregnant women; pregnancy itself does not appear to have an adverse effect on the disease process. There is no need for therapeutic abortion. Stage by stage, the prognosis of breast carcinoma in pregnancy is similar to that of non-pregnant controls. With careful counseling, further pregnancy can be planned after 2-3 years in selected cases.

REFERENCES

1. Kuerer HM, Cunningham JD, Brower ST, Tartter PI. Breast carcinoma associated with pregnancy and lactation. Surg Oncol 1997;6:93-8.
2. Betson JR, Golden ML. Cancer and pregnancy. Am J Obstet Gynecol 1961;81:718-28.
3. Donegan WL. Cancer and pregnancy. CA Cancer J Clin 1983;33:194.
4. Gemignani ML, Petrek JA. Breast cancer during pregnancy: Diagnostic and therapeutic dilemmas. Adv Surg 2000;34:273-86.
5. Di Fronzo LA, O'Connell TX. Diagnosing and Treating Breast Cancer in the Pregnant Woman. Medscape Womens Health 1997;2:1.
6. Murray EM, Werner ID. Pregnancy and abortion in breast cancer patients: Two case reports and a literature review. S Afr Med J 1997;87:1538-9.
7. Puckridge PJ, Saunders CM, Ives AD, Semmens JB. Breast cancer and pregnancy: A diagnostic and management dilemma. *The Lancet* 1999;354:1846-50.
8. Jereczek B. Breast cancer during pregnancy. Ginekol Pol 1995;66:480-3.
9. Antonelli NM, Dotters DJ, Katz VL, Kuller JA. Cancer in pregnancy: A review of the literature- Part I. Obstet Gynecol Surv 1996;51:125-34.
10. Fiorica JV. Special problems. Breast cancer and pregnancy. Obstet Gynecol Clin North Am 1994;21:721-32.
11. DiFronzo LA, O'Connell TX. Breast cancer in pregnancy and lactation. Surg Clin North Am 1996;76:267-78.
12. Hoover HC Jr. Breast cancer during pregnancy and lactation. Surg Clin North Am 1990;70:1151-63.
13. Perez CA, Taylor ME. Breast: Stage Tis, T1 and T2 Tumors. *In*: Perez CA, Brady LW, editors. Principles and practice of Radiation Oncology. Philadelphia: Lipincott-Raven 1998:1390-2.
14. Anderson JM. Mammary cancers and pregnancy. Br Med J 1979;1:1124-7.
15. Nugent P, O'Connell TX. Breast cancer in pregnancy. Arch Surg 1985;120:1221-4.
16. King RM, Welch JS, Martin JL. Carcinoma of the breast associated with pregnancy. Surg Gynecol Obstet 1985;160:228-32.
17. Petrek JA, Dukoff R, Rogatko A. Prognosis of pregnancy-associated breast cancer. Cancer 1991;67:869-72.
18. Ribeiro G, Jones DA, Jones M. Carcinoma of the breast associated with pregnancy. Br J Surg 1986;73:607-9.
19. Canter JW, Oliver GC, Zaloudek CJ. Surgical diseases of the breast during pregnancy. Clin Obstet Gynecol 1983;26:853-64.
20. Cheek JH. Cancer of the breast in pregnancy and lactation. Am J Surg 1973;126:729-31.
21. Holleb AI, Farrow JH. The relation of carcinoma of the breast and pregnancy in 283 patients. Surg Gynecol Obstet 1962;115:65-71.
22. Hoover HC. Carcinoma of the breast in pregnancy and lactation. *In*: Bland KI, editor. The Breast: Comprehensive Management of Benign and Malignant Diseases. Philadelphia: WB Saunders 1991.
23. Peters MV. The effect of pregnancy in breast cancer. *In*: Forrest AP, Kunkler PB, editors. Prognostic Factors in Breast Cancer. Baltimore: Williams and Wilkins 1968.
24. Shivvers SA, Miller DS. Preinvasive and invasive breast and cervical cancer prior to or during pregnancy. Clin Perinatol 1997;24:369-89.

25. Marchant DJ. Breast cancer in pregnancy. Clin Obstet Gynecol 1994;37:993-7.
26. Harris JR, Morrow M, Bonadona G. Cancer of the breast. *In*: De Vita VT, Hellman S, Rosenberg SA, editors. Cancer: Principles and Practice of Oncology, 4th Ed. Philadelphia: JB Lippincott 1993.
27. Applewhite RR, Smith LR, DeVicenti F. Carcinoma of the breast associated with pregnancy and lactation. Am Surg 1973;39:101-4.
28. Clark RM, Reid J. Carcinoma of the breast in pregnancy and lactation. Int J Radiat Oncol Biol Phys 1978;4:693-8.
29. Crosby CH, Barclay TH. Carcinoma of the breast: Surgical management of patients with special conditions. Cancer 1971;28:1628-36.
30. Gwyn KM, Theriault RL. Breast cancer during pregnancy: Current treatment options. Oncol 2000;1:239-43.
31. Moore HC, Foster RS Breast cancer and pregnancy. Semin Oncol 2000;27:646-53.
32. Parente JT, Amsel M, Lerner R, Chinea F. Breast cancer associated with pregnancy. Obstet Gynecol 1988;71:861-4.
33. August DA, Sondak VK. Breast. *In*: Greenfield LJ, editor. Surgery-Scientific Principles and Practice. Philadelphia: Lipincott-Raven 1997:1357-415.
34. Tabbarah HJ. Cancer and Pregnancy. *In*: Haskell CM, editor. Cancer Treatment. Philadelphia: WB Saunders 2001:425-34.
35. Novotny DB, Maygarden SJ, Shermer RW. Fine needle aspiration of benign and malignant breast masses associated with pregnancy. Acta Cytol 1991;35:676-86.
36. Liberman L, Giess CS, Dershaw DD. Imaging of pregnancy associated breast cancer. Radiology 1994;191:245-8.
37. Barnavon Y, Wallack MK. Management of the pregnant patient with carcinoma of the breast. Surg Gynecol Obstet 1990;171:347-52.
38. Woo JC, Yu T, Hurd TC. Breast cancer in pregnancy: A literature review. Arch Surg 2003;138:91-9.
39. Max MH, Klamer TW. Pregnancy and breast cancer. South Med J 1983;76:1088-90.
40. Byrd BF, Bayer DS, Robertson JC. Treatment of breast tumors associated with pregnancy and lactation. Ann Surg 1962;155:940.
41. Finley JL, Silverman JF, Lannin DR. Fine-needle aspiration cytology of breast masses in pregnant and lactating women. Diagn Cytopathol 1989;5:255-9.
42. Gallenberg MM, Loprinzi CL Breast cancer and pregnancy. Semin Oncol 1989;16:369-76.
43. Elledge RM, Ciocca DR, Langone G. Estrogen receptor, progesterone receptor, and HER-2/neu protein in breast cancers from pregnant patients. Cancer 1993;71:2499-506.
44. Keleher AJ, Theriault RL, Gwyn KM, et al. Multidisciplinary management of breast cancer concurrent with pregnancy. J Am Coll Surg 2002;194:54-64.
45. Petrek JA. Breast cancer during pregnancy. Cancer 1994;74: 518-27.
46. Leveque J, Giono A, Poulain P, et al. Breast cancer associated with pregnancy:Nine case reports, review of the literature and current update. J Gynecol Obstet Biol Reprod 1992;21:616-24.
47. Melmed AP. Anesthesia Principles and Techniques in Pregnancy. *In*: Cherry SH, editor. Medical, surgical and gynecological complications of pregnancy. Baltimore: Williams and Wilkins 1985:664-87.
48. Holmes FA. Breast cancer during pregnancy. Cancer Bull 1994;46:400-11.
49. Brent RL. The effect of embryonic and fetal exposure to X-ray, microwaves and ultrasound: Counseling the pregnant and non-pregnant patient about these risks. Semin Oncol 1989;16:347-68.
50. Miller R, Mulvihill S. Small head size after atomic radiation. Teratology 1976;14:355-7.
51. Doll DC, Ringenberg S, Yarbo JW. Antineoplastic agents and pregnancy. Semin Oncol 1989;16:337-46.
52. Shapira DV, Chudley AE. Successful pregnancy following continuous treatment with combination chemotherapy before conception and throughout pregnancy. Cancer 1984;54:800-3.
53. Hornstein E, Skornick Y, Rozin R. The management of breast carcinoma in pregnancy and lactation. J Surg Oncol 1982;21:179-82.
54. Berry DL, Theriault RL, Holmes FA, et al. Management of breast cancer during pregnancy using a standardized protocol. J Clin Oncol 1999;17:855-61.
55. Sweet DL, Kinzie J. Consequences of radiotherapy and antineoplastic therapy for the fetus. J Reprod Med 1976;17:241-6.
56. Isaacs JH. Cancer of the breast in pregnancy. Surg Clin North Am 1995;75:47-51.
57. Merkel DE. Pregnancy and breast cancer. Semin Surg Oncol 1996;12:370-5.
58. Lanids SH, Murray T, Bolden S, et al. Cancer statistics, 1998. CA Cancer J Clin 1998;48:6-29.
59. Sutton R, Buzdar AU, Hortobagyi GN. Pregnancy and offspring after adjuvant chemotherapy in breast cancer patients. Cancer 1990;65:847-50.
60. Danforth DN Jr. How subsequent pregnancy affects outcome in women with a prior breast cancer. Oncology 1991;11:23-31.
61. Malamos NA, Stathopoulos GP, Keramopoulos A, et al. Pregnancy and offspring after the appearance of breast cancer. Oncology 1996;53:471-5.
62. Gelber S, Coates AS, Goldhirsch A, et al. International Breast Cancer Study Group:Effect of pregnancy on overall survival after the diagnosis of early-stage breast cancer. J Clin Oncol 2001;19:1671-5.
63. Sanders JE, Hawley J, Levy W, et al. Pregnancies following high-dose cyclophosphamide with or without high-dose busulfan or total-body irradiation and bone marrow transplantation. Blood 1996;87:3045-52.
64. Cammisuli F, Catania V, Santuccio A, Mirone I, Pagano P, Cavallaro A. Breast carcinoma in pregnancy: A clinical case. Ann Ital Chir 2002;73:317-21.
65. Barrat J, Marpeau L, Demuynck B. Breast cancer and pregnancy. Rev Fr Gynecol Obstet 1993;88:544-9.
66. Harvey JC, Rosen PP, Ashikari R, et al. The effect of pregnancy on the prognosis of carcinoma of the breast following radical mastectomy. Surg Gynecol Obstet 1981;153:723-5.
67. von Schoultz E, Johansson H, Wilking N, et al. Influence of prior and subsequent pregnancy on breast cancer prognosis. J Clin Oncol 1995;13:430-4.
68. Kroman N, Jensen MB, Melbye M, et al. Should women be advised against pregnancy after breast-cancer treatment? Lancet 1997;350:319-22.
69. Mignot L. Cancer of the breast and pregnancy: The point of view of the breast cancer specialist. Bull Cancer 2002;89:772-8.
70. Clark RM, Chua T. Breast cancer and pregnancy: The ultimate challenge. Clin Oncol (R Coll Radiol) 1989;1:11-8.
71. Mignot L, Morvan F, Berdah J, et al. Pregnancy after treated breast cancer: Results of a case-control study. Presse Med 1986;15: 1961-4.
72. Ariel IM, Kempner R. The prognosis of patients who become pregnant after mastectomy for breast cancer. Int Surg. 1989;74:185-7.
73. Sankila R, Heinavaara S, Hakulinen T. Survival of breast cancer patients after subsequent term pregnancy: "Healthy mother effect." Am J Obstet Gynecol 1994;170:818-23.