

Risk of Breast Cancer due to Hyperprolactinemia caused by Antipsychotics (Neuroleptics)

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ABSTRACT

Breast cancer is the most common cancer in females, and is the second most common cause of death. There are several factors which increase a woman's risk for the development of breast cancer. Some reports suggest that neuroleptics and other dopamine antagonists increase the risk of breast cancer due to hyperprolactinemia. There are other reports which suggest that they may decrease the risk of cancer especially rectum, colon and prostate. Additionally, there is evidence that patients with Parkinson's disease have lower rates of breast cancer and other types of malignancies.

KEYWORDS: Hyperprolactinemia, Antipsychotics, Breast cancer

Introduction

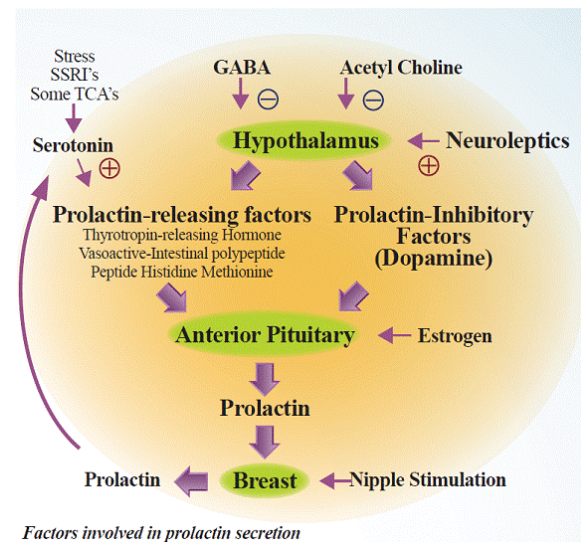
Prolactin is a polypeptide hormone that is secreted by lactotrophs of the anterior pituitary gland. Prolactin secretion shows a circadian rhythm¹, with highest levels occurring during the night and the nadir occurring during the afternoon and evening. The best known function of prolactin is the stimulation and maintenance of lactation.

Normal basal levels of serum prolactin are approximately 20 to 40 ng/ml in women (depending on the phase of their menstrual cycle), and 15 ng/ml in men. However, these concentrations can also vary with age. Hyperprolactinemia is diagnosed when serum prolactin concentrations are >20-25 ng/ml (400-500 mU/l) on two separate occasions³.

Hyperprolactinemia is the most common disorder of the hypothalamic-pituitary-gonadal (HPG) axis⁴ and can have physiological causes - pregnancy, nursing, sleep, stress, sexual intercourse or pathological causes - tumor called prolactinoma. Multiple factors are involved in prolactin secretion (Figure 1). However, hyperprolactinemia is also a common side-effect of traditional antipsychotics (e.g. haloperidol) and is associated with the use of some newer second generation agents^{2, 6}.

The prevalence of hyperprolactinemia is low in the general population (0.4%), but it can be as high as 9 to 17 % in women with reproductive disorders. The disease occurs more frequently in women than in men, multiple signs and symptoms associated with hyperprolactinemia (Table 1).

Multiple variables affect probability of development of breast cancer (Table 2) and a number of important factors determine the risk for breast cancer, and the most important of these seem to be related to estrogen and possibly prolactin (Table 3).



Factors involved in prolactin secretion

Figure 1: Factors involved in Prolactin secretion

Table 1: Signs and Symptoms of Hyperprolactinemia

- Gynaecomastia
- Galactorrhoea
- Infertility
- Menstrual irregularities: oligomenorrhoea, amenorrhoea
- Sexual dysfunction: decreased libido, impaired arousal, impaired orgasm
- Acne and hirsutism in women (due to relative androgen excess compared with low estrogen levels)
- Behavioural effects
- Decreased bone mineral density (BMD) which may lead to increased risk of osteoporosis.

Table 2: Probability of Developing Breast Cancer³²

Risk of Breast cancer		
Variables	Increased	Decreased
Age	Older	Younger
Socioeconomic status	Higher	Lower
Family history of breast cancer	Present	Absent
Racial	Caucasian	Oriental
Geographic	America	Asia
Marital status	Single	Married
Age at first pregnancy	Older	Younger
History of multiple pregnancies	Present	Absent
Age at menarche	Younger	Older
Age at natural menopause	Older	Younger
Artificial menopause	Absent	Present

Table 3: Epidemiology of breast cancer⁷

- Age of menarche
- Late pregnancy
- Obesity
- Caucasian females have slightly higher incidence
- The highest incidence of breast cancer occurs after age 35, with 83% of the cases occurring after age 50 and only 1.5% under age 30
- 1 in 11 women will develop breast cancer sometime during their lifetime
- The highest incidence of breast cancer in the US is found in the northeastern part of the country
- The women with previous cancer of one breast are at risk for cancer in the opposite breast
- A woman whose natural menopause occurs before age 45 has only half the breast cancer risk of those whose menopause occurs after the age of 55⁷.

Methods

Pubmed.gov searched by using keywords

Antipsychotics and Hyperprolactinemia

Hyperprolactinemia is caused by these agents by blocking D2 receptors on lactotrophs and thus preventing inhibition of prolactin secretion. Furthermore, it has been suggested that the degree of elevation of prolactin correlates with the degree of occupation of D2 receptors in excess of 50%⁸.

Most studies have shown that conventional antipsychotics are associated with a two to tenfold increase in prolactin levels^{9, 10}. In general, second generation antipsychotics produce a lower increase in prolactin than conventional agents. Among second generation antipsychotics associated with increased prolactin are amisulpride, zotepine and risperidone^{11, 12, 13}.

Antipsychotic induced Hyperprolactinemia and Breast cancer

Prolactin is known to increase the incidence of spontaneously occurring mammary tumors in mice¹⁴ and increase the growth of established carcinogen-induced mammary tumors in rats¹⁵.

Prolactin and other sex hormones such as, estradiol and progesterone are important in normal mammary gland growth and development as well as lactation. Both animal and *in vitro* data suggest that prolactin is involved in tumorigenesis by promoting cell proliferation, increasing cell motility, and improving tumor vascularization. Whereas prolactin and its receptor are found in normal and malignant tissues, concentrations of both are generally higher in malignant tissue¹⁶.

Several studies have linked hyperprolactinemia to an increased risk of breast cancer in women^{17, 18}. Mechanisms that have been suggested to explain this possible action of prolactin include the increased synthesis and expression of prolactin receptors in malignant breast tissue and a prolactin-induced increase in DNA synthesis in breast cancer cells *in vivo*¹⁸.

One of the hypothesized roles of prolactin in the development of mammary tumors is to create mammary gland conditions favorable for the action of carcinogens through its stimulation of the rate of mammary gland DNA synthesis, a measure of the frequency of mammary gland cell division¹⁹.

Several epidemiological studies have investigated whether female psychiatric patients receiving treatment with antipsychotics have a higher incidence of breast cancer but results have been conflicting. However, the most recent and methodologically strong study, found that antipsychotic dopamine receptor antagonists conferred a small but significant risk of breast cancer. This study had a retrospective cohort design and compared women who were exposed to prolactin-raising antipsychotics with age-matched women who were not²⁰.

Conversely, other studies have shown no correlation between hyperprolactinemia and breast cancer^{21, 22}. Furthermore, as most breast cancers are thought to be fueled by estrogen²³, and hyperprolactinemia causes estrogen deficiency²⁴, it is perhaps surprising that hyperprolactinemia has been linked with an increased risk of breast cancer. Indeed, post-operative hyperprolactinemia in breast cancer patients has been shown to improve disease free and overall survival. Obviously, more studies are necessary to define any possible links between hyperprolactinemia and breast cancer.

In view of these problems it would be of interest to go around the contentious issue of possible carcinogenic effects of dopamine antagonists using a classical condition of dopamine loss or attenuation as in Parkinson's disease (PD). Using computerized registers of death data of the National Center of Health Statistics for years 1991 through 1996, estimated

12,430,473 deaths of persons over forty, and extracted 144,364 cases with PD. Tellingly, PD patients showed a highly significant reduction of overall cancer incidence. PD resistance to breast cancer might conceivably be attributed to dopaminergic treatment antagonizing hyperprolactinemia^{26, 27, 28}.

Another recent study showed that dopaminergic therapy inhibits angiogenesis thereby acting as an anti-tumor agent²⁹.

Epidemiological studies of women who have received prolactin-releasing drugs such as reserpine and perphenazine have not disclosed increased risk³⁰.

Antipsychotic induced Hyperprolactinemia and Other cancers

Antipsychotics have been hypothesized to account for the reduced cancer occurrence observed in patients with schizophrenia in a number of studies. This reduction has been found primarily in men in smoking-related cancers, and in prostate and rectal cancer.

In addition, a study found a reduced risk of rectal cancer in both men and women as well as indications of a reduced risk of colon and prostate cancer in this population-based cohort of neuroleptic users. Reassuringly, they observed no increased risk of breast cancer in female users³¹.

Comments and recommendations

- Hyperprolactinemia results from treatment with any drug that disrupts dopaminergic function on the HPG axis and is not limited to the use of antipsychotics.
- Management of supposed anti-psychotic associated hyperprolactinemia should exclude all other causes, involve regular monitoring of adverse effects and include a regular risk-benefit discussion with patient.
- Switching the patient to prolactin-sparing antipsychotic (i.e. Aripiprazole, Olanzapine, Quetiapine or Clozapine) usually proves effective, though there is also a risk of relapse.
- It seems prudent to avoid prescribing prolactin-raising antipsychotics in patients with past history or family history of breast cancer.
- It is premature to mandate warning patients of an unknown and undemonstrated increase in the risk of developing breast cancer associated with neuroleptic treatment.
- Before initiating antipsychotic treatment a careful examination of patient is necessary.
- One should examine the patient for evidence of sexual adverse events, including menorrhagia, amenorrhoea, galactorrhoea and erectile/ejaculatory dysfunction. If evidence of any such effects is found, then the patient's prolactin level should be measured.

- Patient history, physical examination, pregnancy test, thyroid function test, blood urea and creatinine level can help determine if other etiologies are responsible.
- Presence of headache and visual field defects is suggestive of a sellar space-occupying lesion (MRI indicated), but the absence of these features does not exclude such pathology.
- History of menstrual cycling (duration, amount and intervals of menstruation) as well as lactation and sexual functioning should be taken before antipsychotic medication is initiated.
- Obtain a pretreatment prolactin level, which one can compare with subsequent samples if the patient develops symptoms associated with relatively modest hyperprolactinemia.
- The risk-benefit ratio for treatment of antipsychotic-induced hyperprolactinemia needs to be assessed on an individual basis.
- If there is doubt about the cause of the hyperprolactinemia, patient should be referred to an endocrinologist.

Current recommendation

A rise in prolactin concentration should not be of concern unless complications develop, and until such time no change in treatment is required.²⁰

Conclusions

There is no definitive data suggesting increased risk of breast cancer available at this time, thus author concludes:

- Further prospective studies are needed in this area, with large number of patients, before a more definitive answer can be provided.
- Detection of existing mammary tumor by breast examination or studies (mammogram) is recommended prior to administration of neuroleptics.
- Development of newer antipsychotic drugs that do not increase serum prolactin level may be indicated.

Strengths

- Each article found by search term was reviewed
- Data were extracted from each article to find answer of research question
- Pubmed.gov is a huge database for search.

Limitations

- This literature review has been conducted by a single author, thus bias on part of author cannot be ruled out
- Author was limited by time to review articles available in other databases.

Key Points

- Most studies report no increased risk of breast cancer associated with use of these medications.
- Only one study reported a positive correlation between neuroleptic induced hyperprolactinemia and increased risk of breast cancer.
- Other studies report inconclusive data.
- At this time we do not have definitive data suggesting increased risk of breast cancer secondary to hyperprolactinemia caused by antipsychotics.
- Further prospective studies are desirable.
- Author concludes that thorough screening of patient should be best

Competing Interests

None declared

Author Details

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