

ANTIPSYCHOTIC TREATMENT, PROLACTIN, AND BREAST TUMORIGENESIS

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SUMMARY

Background: Over the last decades prolactin (PRL) has gained attention for its possible role in breast tumorigenesis. As all antipsychotics (although differences with respect to PRL elevation are large) have the propensity to induce hyperprolactinemia (HPRL), questions have arisen concerning the influence of PRL-elevating antipsychotic medications on breast cancer risk.

Subjects and methods: A literature search (until January 2016), using the MEDLINE database, was conducted for English-language published clinical studies to identify and synthesize data of the current state of knowledge concerning the relationship between HPRL, breast cancer risk (factors) and antipsychotic medication.

Results: Results of human prospective studies evaluating the relationship between pre-diagnostic circulating PRL levels and breast cancer risk are limited, equivocal and only correlational. Associations between higher circulating PRL levels and other breast cancer risk factors than nulliparity and hormone therapies mostly have been negative for both pre- and postmenopausal women. Until today, no causal link between (chronic) administration of antipsychotics and breast tumorigenesis in humans has been demonstrated. Finally, several reports describe mechanisms of cancer protection with the PRL hormone as well as with antipsychotic medication.

Conclusion: The role of PRL in breast carcinogenesis therefore remains unclear, unconfirmed, yet controversial. Antipsychotics should not be withheld for breast cancer prevention reasons to patients in need of this sometimes life-saving medication, even if classical breast cancer risk factors are present.

Key words: breast cancer – prolactin – antipsychotics

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INTRODUCTION

Breast cancer is one of the most commonly diagnosed cancers (one in eight women will be diagnosed with breast cancer during their lifetime) and the leading cause of cancer death among females (Anothaisintawee et al. 2013, Ferlay et al. 2010, 2012, Matsen & Neumayer 2013). Although breast cancer does occur in men as well, male breast cancer is rare (Desantis et al. 2014, Ruddy & Winer 2013).

Breast cancer is not a single biological entity but a heterogeneous disease (Hachim et al. 2016, Litznerburger & Brown 2014). Several genetical and molecular subtypes of breast cancer with a distinctly different survival outcome and treatment response have been identified, including (but not limited to) luminal A, luminal B, human epidermal growth factor receptor (HER)2- overexpressing, and triple negative cancers (Barnard et al. 2015, Boyle 2012, Guiu et al. 2012, Hachim et al. 2016, Litznerburger & Brown 2014, Ringnér et al. 2013, Weigelt & Reis-Filho 2009).

A range of risk factors for the development of breast cancer have been established (Barnard et al. 2015, Deroo et al. 2011, Gathani et al. 2014, Gaudet et al.

2013, Jacobson et al. 2010, National Cancer Institute 2016, Tworoger & Hankinson 2008, Venkitarama 2014) (Table 1). Over the last decades prolactin (PRL) has gained attention for its possible role in breast tumorigenesis (da Silva et al. 2015, Froes Brandao et al. 2016, Tikk et al. 2014a). PRL is a neuroendocrine polypeptide hormone that is mainly synthesized in, and released into the blood circulation from lactotroph cells of the anterior lobe of the pituitary gland (i.e. the adenohypophysis) (Booth et al. 2015, Chen 2015, Peuskens et al. 2014). In addition to the adenohypophysis several other extra-pituitary sites, including the mammary gland, physiologically secrete PRL (Ben-Jonathan et al. 2002, 2006, Muthuswamy 2012, Oakes et al. 2008, Peuskens et al. 2014), meaning that PRL reaches the breast both from the systemic circulation as well as from local sources (Ben-Jonathan et al. 2002, LaPensee & Ben-Jonathan 2010). While the role of PRL in the normal development of the mammary gland, breast enlargement during pregnancy and the induction and maintenance of milk production during lactation is well established, its role in breast cancer remains unclear and controversial (Hachim 2016, Haddad & Wieck 2004, Peuskens et al. 2014).

Table 1. Breast cancer risk factors (Barnard et al. 2015, Deroo et al. 2011, Gathani et al. 2014, Gaudet et al. 2013, Jacobson et al. 2010, National Cancer Institute 2016, Tworoger & Hankinson 2008, Venkitarama 2014)

Age (a woman's risk of developing the disease increases as she gets older)
Alcohol use
Carrying breast cancer susceptibility genes (e.g., BRCA1 and BRCA2 mutations confer a 60% to 80% life-time risk for the development of breast cancer)
Delayed childbearing (having a first full-term pregnancy after age 30)
Diabetes mellitus
Early menarche (beginning to menstruate before age 12)
Hormone replacement therapy (HRT) (also called menopausal hormone therapy or MHT)
Lack of breastfeeding
Late menopause (starting menopause after age 55)
Low physical activity
Mammographic breast density (having dense breast)
Nulliparity (never having been pregnant/children),
Obesity
Previous breast biopsy
Personal or family history of breast or ovarian cancer
Race (more often in White women, compared to South Asian and Black women)
Radiation therapy to the breast
Smoking (?)

Like normal mammary gland development, breast carcinogenesis mostly is a hormonally dependent process (Lee & Ormandy 2012). Therefore, female reproductive hormones estrogen and progesterone, and possibly the PRL hormone, can have a major impact on breast cancer risk/growth and breast cancer cell movement (Briskin & O'Malley 2010, da Silva et al. 2015, LaPensee & Ben-Jonathan 2010, Lee & Ormandy 2012, Perks et al. 2004). As the biological activities of PRL are mediated by specific membrane receptors (i.e. PRL receptor, PRLR) (Chen 2015), effects of this hormone on breast cancer have been proposed to be mediated by interaction with this receptor (Nitze et al. 2013), which is found in up to 80-90% of breast cancer cells (LaPensee & Ben-Jonathan 2010).

The possible role of PRL in breast tumorigenesis has raised questions about the impact of antipsychotic-induced hyperprolactinemia (HPRL) (usually defined as fasting levels >20 ng/ml in men, and >25 ng/ml in women) on breast cancer risk. Under normal physiological conditions pituitary PRL synthesis and secretion is tonically inhibited by the hypothalamus, mediated by a number of PRL inhibitory factors of which dopamine is the most important one (Muthuswamy 2012, Oakes et al. 2008, Peuskens et al. 2014). A blockade of dopamine D2 receptors (D2R) counteracts the tonic inhibitory effect of dopamine on

the PRL secretion, resulting in disinhibition of PRL secretion. The stronger the dopamine D2R blockade, the higher the PRL elevation (Peuskens et al. 2014). Antipsychotics have a D2R-blocking effect and therefore elevate the secretion of PRL (Peuskens et al. 2014). These medications are commonly divided into 2 categories based on their mechanism of action and clinical profile. First generation antipsychotics (FGA), also known as typical antipsychotics, block dopamine receptors and, as a class, are associated with extrapyramidal side effects. Second generation antipsychotics (SGA) antagonize both dopamine and serotonin receptors but affect dopamine to a lesser degree than FGA, resulting in fewer extrapyramidal side effects. However, these agents carry side effects (e.g., metabolic) of their own (Stubbs et al. 2016, Vancampfort et al. 2015). Although all antipsychotics have the propensity to induce HPRL, differences between antipsychotic drugs with respect to PRL elevation are large (Peuskens et al. 2014). The highest rates of HPRL are consistently reported in association with the FGA and the SGA amisulpride, risperidone and paliperidone, while the SGA aripiprazole and quetiapine have the most favourable profile with respect to this outcome (Peuskens et al. 2014) (Table 2). Because of the widespread (off-label) use of antipsychotic medication in the clinical field (antipsychotics not only remain the cornerstone of pharmacological treatment in patients with schizophrenia or other psychotic disorders, but are also frequently used for a wide range of other psychiatric or medical conditions), this topic certainly has a relevance for clinical practice.

Table 2. Prolactin side-effect profile of second generation antipsychotics (Peuskens et al. 2014)

	Prolactin elevation
Amisulpride	+++
Aripiprazole	0
Asenapine	+
Clozapine	+
Iloperidone	+
Lurasidone	++
Olanzapine	++
Paliperidone	+++
Quetiapine	+/-
Risperidone	+++
Sertindole	+
Ziprasidone	++

0 = minimal to no risk; +/- = minimal risk; + = low risk; ++ = moderate risk; +++ = high risk

Three important issues are discussed in this review: (1) is there evidence that elevated plasma PRL levels increase the risk of breast cancer? (2) does a relationship exist between elevated PRL levels and established breast cancer risk factors?, and (3) is there evidence that, particularly PRL-elevating, antipsychotic medication enhances breast cancer risk?

SUBJECTS AND METHODS

A systematic search (until January 2016), using the MEDLINE database, was conducted for English-language published clinical trials to synthesize the results concerning the current state of knowledge about breast cancer risk (factors) and its relationship to HPRL and antipsychotic medication. For the association between breast cancer risk and HPRL, we limited ourselves to prospective studies. Retrospective studies have little scientific value because they assess PRL levels after the woman had been diagnosed with breast cancer and introduce the potential for reverse causality bias. For the association between breast cancer risk and antipsychotic medication, case report studies were excluded. The following key words were used in various combinations: ‘breast cancer’, ‘risk factor’, ‘prolactin’, ‘prolactinoma’, ‘prospective’, ‘antipsychotic’, ‘neuroleptic’, ‘risperidone’, ‘olanzapine’, ‘quetiapine’, ‘clozapine’, ‘aripiprazole’, ‘amisulpride’, ‘sulpiride’, ‘paliperidone’, ‘sertindole’, ‘ziprasidone’, ‘lurasidone’, ‘iloperidone’, ‘asenapine’, ‘haloperidol’, ‘phenothiazines’, and ‘butyrophenones’. We reviewed the reference lists of identified studies and reviews to detect any additional and potentially important articles.

RESULTS

Do elevated plasma PRL levels increase the risk of breast cancer?

Data related to the association between pre-diagnostic circulating PRL levels and breast cancer risk are sparse. Until now, only two large database and five

small prospective studies (Hankinson et al. 1999; Helzlsouer et al. 1994, Kabuto et al. 2000, Kwa et al. 1981, Manjer et al. 2003, Tikk et al. 2014a, 2015, Tworoger et al. 2004, 2006, 2007, 2013, 2015, Tworoger & Hankinson 2008, Wang et al. 1992) have addressed the associations between circulating PRL levels and breast cancer risk in the general population (Table 3). Those involving small sample sizes (maximum 173 breast cancer cases) (Helzlsouer et al. 1994, Kabuto et al. 2000, Kwa et al. 1981, Manjer et al. 2003, Wang et al. 1992) found no statistical significant relationship between PRL levels and breast cancer risk among either pre- or postmenopausal women. Although the larger database studies (The American Nurses’ Health Studies (NHS I/II) and the European Prospective Investigation into Cancer (EPIC) study) have shown that higher circulating PRL levels are associated with an increased breast cancer risk, their findings only partially agree. A pooled analysis, including data sets from the NHS I and NHS II cohorts with new data, found a 40% increased breast cancer risk ($p=0.05$) for premenopausal women with the highest (= upper level of the normal range) versus lowest quartile of PRL concentrations (Tworoger et al. 2007). However, in the EPIC studies a statistically non-significant association between PRL levels and breast cancer risk among premenopausal women was observed (Odds Ratio, $OR=0.70$; 95% Confidence Interval, 95%CI: 0.48–1.03 for invasive breast cancer and $OR=1.30$; 95%CI: 0.80–2.10 for in situ breast cancer) (Tikk et al. 2014a, 2015). With respect to postmenopausal women, a 30% increase in breast cancer risk ($p=0.01$) was demonstrated in the pooled analysis of the NHS cohorts (Tworoger et al. 2007).

Table 3. Overview of Prospective Studies on Prolactin Concentrations and Breast Cancer Risk in Premenopausal and Postmenopausal Women (Hankinson et al. 1999; Helzlsouer et al. 1994, Kabuto et al. 2000, Kwa et al. 1981, Manjer et al. 2003, Tikk et al. 2014a, 2015, Tworoger et al. 2004, 2006, 2007, 2013, 2015, Tworoger & Hankinson 2008, Wang et al. 1992)

LEGEND: CI: Confidence Interval; EPIC: European Prospective Investigation into Cancer; ER: Estrogen Receptor; HRT: Hormone Replacement Therapy; HR: Hazard Ratio; N/A: Not Available; NHS: Nurses’ Health Study; NS: Not Significant; OR: Odds ratio; PR: Progesterone Receptor; PRL: Prolactin; RR: Relative Risk; Italics: statistically significant data; §: Including women with unknown menopausal status

Table 3A. EPIC Database Study

Study	Number of Cases and Controls	Premenopausal - Results	Postmenopausal - Results
Tikk et al. 2015	Premenopausal 86 cases/86 controls Postmenopausal 221 cases/221 controls	$OR=1.30$; 95%CI:0.80–2.10 (top versus bottom tertile)	<i>$OR=1.38$</i> ; 95%CI:1.00–1.91 (top versus bottom tertile) $OR=1.20$; 95%CI:0.82–1.76 (top versus bottom tertile for postmenopausal non-HRT-users) $OR=1.77$; 95%CI:0.98–3.21 (top versus bottom tertile for postmenopausal HRT-users)
Tikk et al. 2014a	Premenopausal 512 cases/512 controls Postmenopausal 1,738 cases/1,738 controls	$OR=0.70$; 95%CI:0.48–1.03 (top versus bottom quartile) $OR=0.70$; 95%CI:0.44–1.09 (ER+ cases) (top versus bottom quartile)	<i>$OR=1.29$</i> ; 95%CI:1.05–1.58 (top versus bottom quartile for all postmenopausal women) $OR=1.11$; 95%CI:0.83–1.49 (top versus bottom quartile for postmenopausal non-HRT-users) <i>$OR=1.45$</i> ; 95%CI:1.08–1.95 (top versus bottom quartile for postmenopausal HRT-users) <i>$OR=1.29$</i> ; 95%CI:1.02–1.63 (ER+ cases) (top versus bottom quartile for all postmenopausal women) $OR=1.12$; 95%CI:0.80–1.57 (ER+ cases) (top versus bottom quartile for postmenopausal non-HRT-users) <i>$OR=1.42$</i> ; 95%CI:1.01–1.99 (ER+ cases) (top versus bottom quartile for postmenopausal HRT-users)

Table 3B. NHS Database Studies

Study	Number of Cases and Controls	Premenopausal - Results	Postmenopausal - Results
Tworoger et al. 2015	Pre-menopausal 241 cases/241 controls Postmenopausal 119 cases/118 controls	RR=0.99; 95%CI:0.71–1.37 (top versus bottom quartile)	RR=1.36; 95%CI:0.93–1.98 (top versus bottom quartile)
Tworoger et al. 2013	PRL collected <10 years before diagnosis 2,468 cases 4,021 controls PRL collected >10 years before diagnosis 953 cases 1,339 controls	RR=1.05; 95%CI:0.82–1.33 (<10 years) (top versus bottom quartile) RR=0.98; 95%CI:0.73–1.32 (<10 years, ER+ cases) (top versus bottom quartile) RR=1.03; 95%CI:0.68–1.56 (>10 years) (top versus bottom quartile) RR=0.81; 95%CI:0.51–1.30 (>10 years, ER+ cases) (top versus bottom quartile)	RR=1.37; 95%CI:1.11–1.69 (<10 years) (top versus bottom quartile) RR=1.52; 95%CI:1.19–1.93 (<10 years, ER+ cases) (top versus bottom quartile) RR=0.93; 95%CI:0.66–1.33 (>10 years) (top versus bottom quartile) RR=0.97; 95%CI:0.65–1.43 (>10 years, ER+ cases) (top versus bottom quartile)
Tworoger & Hankinson 2008	Pooled analysis of approximately 80% of the world's prospective data	RR=1.3; 95%CI: 1.1–1.6 (top versus bottom quartile). Results were similar for premenopausal and postmenopausal women. High PRL levels were associated with a 60% increased risk of estrogen receptor positive tumors	
Tworoger et al. 2007	Pre-menopausal New analysis 377 cases 786 controls Pooled analysis of new data with data sets from the NHS and NHS II cohorts 492 cases 1,001 controls Postmenopausal Pooled analysis of new data with data sets from the NHS and NHS II cohorts 915 cases 1,410 controls	RR=1.3; 95%CI:0.9–1.9 (top versus bottom quartile) RR=1.4; 95%CI:1.0–1.9 (top versus bottom quartile)	RR=1.3; 95%CI:1.1–1.7 (top versus bottom quartile)
Tworoger et al. 2006	Pre-menopausal 316 cases/633 controls	RR=1.5; 95%CI:1.0–2.5 (top versus bottom quartile) Comparable RR=1.9; 95%CI:1.0-3.7 (ER+/PR+ tumors)	N/A
Tworoger et al. 2004	Postmenopausal 851 cases/1,275 controls	N/A	RR=1.34; 95%CI:1.02–1.76 (top versus bottom quartile) RR=1.78; 95%CI:1.28–2.50 (ER+/PR+ tumors) RR=0.76; 95%CI:0.43–1.32 (ER-/PR- tumors) RR=1.94; 95%CI:0.99–3.78 (ER+/PR- tumors)
Hankinson et al. 1999	Postmenopausal 306 cases/448 controls	N/A	Multivariate RR=2.03; 95%CI: 1.24–3.31 (top versus bottom quartile)

This association differed by Estrogen/Progesterone (ER/PR) status, as the relative risk (RR) was found to be significant only for tumors with ER+/PR+ status (RR=1.78; 95%CI: 1.28–2.50) (Tworoger et al. 2007). Although the EPIC study equally found higher serum levels of PRL to be associated with a statistically significant increase in breast cancer risk among postmenopausal women (OR=1.29; 95%CI: 1.05–1.58), this increase in risk seemed to be confined to women who used hormone replacement therapy (HRT) at blood donation (OR=1.45; 95%CI: 1.08-1.95), whereas no statistically significant association was found for non-users of HRT (OR=1.11; 95%CI: 0.83–1.49). They also found no evidence for heterogeneity of the PRL-breast cancer association by receptor status (Tikk et al. 2014a).

Almost all prospective studies have studied the relationship between circulation PRL levels and invasive breast cancer (cancer that invades the surrounding tissues) risk. The association between PRL and in situ breast cancer (malignant cells but without invading the surrounding tissues, also called non-invasive cancer or pre-cancer) risk has received less attention. Nevertheless, a focus on in situ breast cancer offers the advantage of exploring the associations with risk factors that are important early in the carcinogenic process (thus prior to development of invasive breast cancer) (Tikk et al. 2015). Three prospective studies have included subjects with in situ breast cancer (Manjer et al. 2003, Tikk et al. 2015, Tworoger et al. 2013). Of these only two provide estimates separately by in situ versus invasive

Table 3C. Other (Small) Prospective Studies

Study	Number of Cases and Controls	Premenopausal - Results	Postmenopausal - Results
Manjer et al. 2003	Postmenopausal 173 cases/438 controls	N/A	Adjusted OR=1.34; 95%CI: 0.83–2.17 (top versus bottom quartile)
Kabuto et al. 2000	Premenopausal 46 cases/94 controls Postmenopausal 26 cases/56 controls	OR=1.01; 95%CI: 0.02–47.4. For a log10 unit increase	OR=6.45; 95%CI: 0.01–43.9. For a log10 unit increase
Helzlsouer et al. 1994	Premenopausal 21 cases/42 controls	RR=1.1; 95%CI: 0.3–4.1 (top versus bottom tertile)	N/A
Wang et al. 1992	Premenopausal 71 cases/2,596 controls Postmenopausal 40 cases/1,180 controls	RR=1.1; 95%CI: 0.5–2.2 (top versus bottom quintile)	RR=1.6; 95%CI: 0.6–4.7 (top versus bottom quintile)
Kwa et al. 1981	Premenopausal 22 cases For each women who developed breast cancer, ten controls satisfying the matching requirements were available (in three cases only nine controls were available) Postmenopausal 8 cases For each women who developed breast cancer, ten controls satisfying the matching requirements were available (in three cases only nine controls were available)	Not statistically significant (p=0.67)	8 cases Association between elevated plasma PRL levels and subsequent breast cancer is significant (p=0.04) and on average their values were at the 72nd percentile when compared to matched controls

breast cancer. In the Tworoger et al. (2013) study no increased risk has been found for in situ breast cancer among postmenopausal women with the highest versus lowest range of normal PRL levels (OR=1.16; 95%CI: 0.77-1.74). On the other hand, Tikk et al. (2015) found a modest positive association between higher PRL levels and risk of in situ breast cancer among all women (pre- and postmenopausal combined, OR=1.35; 95%CI: 1.04-1.76). No statistically significant heterogeneity was found by menopausal status or HRT use at blood donation. One should be very cautious when interpreting prospective studies on the occurrence of in situ carcinoma, since this tumor is nearly always asymptomatic and mainly detected by microcalcifications on screening mammographies. The incidence of in situ carcinoma thus mainly depends on how actively the women have been screened. This information was generally lacking in the publications here cited.

Some studies (Tikk et al. 2015, Tworoger et al. 2013) found a differential association by time between blood collection and diagnosis, while others (Tikk et al. 2014a) did not. Tikk et al. (2015) found that the relationship between PRL and in situ breast cancer was confined to tumors diagnosed within the first 4 years from blood donation. They observed that higher concentrations of PRL were significantly associated with in situ breast cancer less than 4 years since blood donation (OR=1.78; 95%CI: 1.12-2.84), but not with breast cancer diagnosed 4 or more years since blood donation (OR=1.09; 95%CI: 0.77-1.55). Similarly, Tworoger et al. (2013), in their 20-year prospective study, observed that PRL was only associated with breast cancer risk when assessed within 10 years before diagnosis, but no associations were observed for blood

sampled 10 to 20 years before diagnosis. This was in contrast to what was observed for estradiol and testosterone in the same population, in which levels predicted risk for up to 16 to 20 years.

Another way to address the question whether circulating levels of PRL are important for the development of breast cancer, is to study patients with a tumor secreting PRL (prolactinoma). Due to delays in diagnosis, these patients often have been exposed to increased PRL levels for months or even years and therefore are an interesting population for investigating the association between HPRL and breast cancer risk. Although there is a paucity of such data, two large cohort studies (Berinder et al. 2011, Dekkers et al. 2010) of patients treated for idiopathic HPRL or prolactinomas did not find any increased risk of breast cancer.

A third interesting approach to explore the contentious issue of possible carcinogenic effects of PRL is to look at patients with Parkinson's disease (PD) who have low dopamine levels (Aziz et al. 2011, Lalonde & Myslobodsky 2003, Rugbjerg et al. 2012). On the basis of this observation, one would expect to find high PRL levels and a positive association between PD and breast cancer. However, results are inconsistent (Connolly & Lang 2014, Lalonde & Myslobodsky 2003).

Taken together, we can conclude that results of human prospective studies are limited and equivocal (with risk ratios ranging from 0.70 to 1.9 for premenopausal women, and from 0.76 to 2.03 for postmenopausal women). Moreover, since the available data are correlational, the question of whether or not elevated PRL levels actually cause breast cancer remains unanswered. A recent review therefore stated that if PRL increases breast cancer risk, it is probably a

factor of (at most) modest magnitude. Well-known breast cancer risk factors probably are of greater relevance than PRL when considering breast cancer risk and mortality (De Hert et al. 2016).

Does a relationship exist between prolactin and established breast cancer risk factors?

A number of studies have evaluated the association between PRL levels and several well-established breast cancer risk factors. Only the associations with nulliparity and hormone therapies (oral contraceptives, OC and HRT) have been firmly confirmed. It has been found that PRL levels among parous women are lower than those among nulliparous women (Hietala et al. 2008, Tikik et al. 2014b). Although several studies (Ingram et al. 1990, Tikik et al. 2014b, Wang et al. 1988) have found a gradual decrease in PRL levels with increasing number of full-term pregnancy, in others (Eliassen et al. 2007, Musey et al. 1987, Nagata et al. 2011) the parity associated decrease was only related to the first full-term pregnancy. Nevertheless, data have demonstrated that women that have given birth one or more times have 15-50% lower PRL levels than nulliparous women, with the majority of this decrease following the first full-term pregnancy (Eliassen et al. 2007, Faupel-Badger et al. 2010a, Tworoger & Hankinson 2008). Mechanisms of the reduced PRL secretion after pregnancy are currently still unclear (Tikik et al. 2014b). Some studies have found that in parous women post-lactational PRL levels are lowered by longer breast-feeding duration of the first child, with no substantial effect on feeding subsequent children (Hietala et al. 2008). However, other studies (Eliassen et al. 2007, Tikik et al. 2014b) suggest that this association may be diminished with time, if present at all. Some reports have demonstrated a positive association between PRL levels and OC (Clevenger et al. 2003, Faupel-Badger et al. 2010a) or HRT use (Tikik et al. 2014a, 2014b). Significantly higher levels of circulating PRL have been demonstrated among postmenopausal women who were currently using HRT, compared with women who did not use HRT. Whether these higher levels of PRL depend on the composition/type of the used HRT regimen is less clear (Tikik et al. 2014b).

In conclusion, associations between higher circulating PRL levels and other breast cancer factor risk than nulliparity and hormone therapies (such as breast cancer-related lifestyle risk factors) mostly have been negative for both pre-and postmenopausal women, even after adjusting for parity (Clevenger et al. 2003, Eliassen et al. 2007, Faupel-Badger et al. 2010a, Greendale et al. 2007, Tikik et al., 2014a, 2014b, Tworoger & Hankinson 2008).

Is there evidence that, particularly PRL-elevating, antipsychotic medication enhances breast cancer risk?

The majority of the studies investigating the influence of antipsychotic medication on breast cancer

risk have considered patients treated with FGA. These studies (Brugmans et al. 1973, Dalton et al. 2006, Kanhouwa et al. 1984, Kelly et al. 1999, Wagner & Mantel 1978) have not found an increased risk of breast cancer, an exception being the cohort study by Wang et al. (2002). These researchers conducted a retrospective cohort study in more than 100,000 women (including psychiatric patients as well as medical patients and patients from nursing homes) in which the relationship between FGA (and the SGA risperidone) and breast cancer risk was investigated. In this study, 52,819 women on dopamine antagonists were compared with 55,289 women who were not on this medication. The authors found that, compared with non-users, women who used antipsychotic dopamine antagonists had a 16% greater risk (adjusted Hazard Ratio=1.16, 95%CI: 1.07–1.26) of developing breast cancer, with a dose-response relationship between larger cumulative dosages and greater risk. However, as stated by the authors, the magnitude of the observed risk, although statistically significant, is small in absolute terms (1,239 cases of breast cancer in the user group versus 1,228 cases in the non-user group), and they estimated there is less than a 14% chance that a dopamine antagonist user who develops breast cancer did so on the basis of her antipsychotic drug use. Moreover, although the power was limited, it is noteworthy that breast cancer risk was statistically significantly increased in those taking phenothiazines (e.g., chlorpromazine, perphenazine), but not butyrophenones (e.g., haloperidol), despite the fact that both FGA classes increase PRL by a similar amount (Holt & Peveler 2011, Madhusoodanan et al. 2010). The authors therefore concluded that their findings “do not warrant changes in patients’ antipsychotic medication regimens” (Wang et al. 2002) (p. 1153). Despite these results, the study by Wang et al. has consistently been cited to demonstrate that antipsychotic medications can induce breast cancer, particularly in female patients with schizophrenia. Hippisley-Cox et al. (2007) tried to determine the risk of six common types of cancer in patients with schizophrenia or bipolar disorder (40,441 incident cases with up to five matched controls per case) and found a 52.2% increase in breast cancer risk in women with schizophrenia, compared with patients without mental health problems. However, only a small association with antipsychotic medication was found. The increase in breast cancer risk was not substantially different in subgroups with (FGA or SGA) and without antipsychotic medication use (adjusted OR=1.55 (95%CI: 1.08–2.23) for users and 1.43 (95%CI: 0.68–3.01) for non-users, both compared with patients without mental health problems). In a large-scale population-based cohort study of all residents in a Danish county, Dalton et al. (2006) found no increased risk for breast cancer among 25,264 FGA users (adjusted Incidence Rate Ratio=0.93; 95%CI: 0.74–1.17), compared with residents of the same Danish county who did not receive such prescriptions. However, their inclusion criteria were very broad (for

example 8,927 included patients had received merely 2-4 prescriptions of antipsychotics and only 8.5% of female antipsychotic users had a diagnosis of schizophrenia), meaning that most of the included patients perhaps did not receive high and/or chronic doses of antipsychotics. In a systematic review of the literature on the potential pro-or anti-cancer activity of antipsychotics, Fond et al. (2012) included 93 studies (in vitro, animal and human studies) considering the effects of antipsychotic drugs (FGA + SGA) on cancer development and found that antipsychotics as a class cannot be considered as a risk factor for breast cancer in humans.

Although SGA, as a group and compared to FGA, are associated with less PRL elevations, there are concerns that the SGA risperidone, amisulpride and paliperidone, which have been associated with a high prevalence of HPRL (Peuskens et al. 2014) (Table 1), may increase the risk of breast cancer. However, results indicate that SGA do not appear to increase the risk of breast cancer. Azoulay et al. (2011) conducted a retrospective cohort study (including 106,362 patients prescribed at least one FGA or SGA) and matched all incident cases of breast cancer up to 10 controls per case. They found that, compared to patients who only used FGA, exclusive users of SGA were not at an increased risk of breast cancer (RR=0.81, 95%CI: 0.63–1.05). These results remained consistent after considering specific SGA known to significantly increase PRL levels, such as risperidone (RR=0.86, 95%CI: 0.60–1.25). These findings were strengthened by the lack of any dose-response association, which considered both cumulative duration of use (patients were exposed for up to 23 years) and cumulative dose. Furthermore, no increased risk was observed in higher risk groups, such as in postmenopausal women.

Thus, on the basis of the available data, it can be concluded that, until now, no causal link between (chronic) administration of antipsychotics and breast tumorigenesis in humans has been shown.

A different, but strongly related issue is whether antipsychotics can also increase the risk of relapse after prior treatment for early breast cancer, or whether it promotes tumor growth in patients with metastatic breast cancer. Despite the absence of controlled studies, the lack of a clear association between antipsychotics and breast tumorigenesis and reports that antipsychotic medications display potential anticancer activity (see further) is reassuring, and suggests that PRL does not influence breast cancer biology importantly. A recent review concluded that, as until today evidence is unconvincing and insufficient, even breast cancer patients may not be deprived of potentially effective antipsychotic medications for serious psychiatric indications and revised medication guidelines are needed to avoid the existing undertreatment of serious psychiatric problems among these patients (Froes Brandao et al. 2016).

DISCUSSION

Besides the fact that the existing evidence concerning a possible relationship between PRL and breast tumorigenesis is limited, equivocal and correlational, thus precluding any claims regarding causality, some other important considerations have to be made.

Firstly, studies examining the relationship between elevated PRL levels and breast cancer risk primarily have used immunoassays to measure PRL concentrations. This method captures multiple PRL isoforms and thus may not reflect the activity of the specific bioactive monomeric PRL hormone (with a molecular mass of 23 kiloDalton, kDA) which is supposed to be most relevant to breast carcinogenesis (Froes Brandao et al. 2016). Although the 23kDA PRL is the most common form of circulating PRL, forms with a higher (or lower, see further) molecular mass, such as the “big” (50-kDA) PRL and the “big-big” (150-kDA) PRL or macroprolactin, are also present, which both are essentially biologically inactive. Moreover, glycosylated 23kDA PRL has a lower biologic activity due to reduced binding to its receptors than the non-glycosylated 23kDA PRL form. In most normal subjects, the 23kDA monomeric PRL accounts for ~65-85% of the total circulating PRL (of which only ~40-65% is non-glycosylated), the 50kDA “big” PRL accounts for ~10-20%, while the 150kDA “big-big” PRL or macroprolactin contributes <10%. However in case of HPRL, the level of any or all of these forms can be raised and their relative proportions can vary considerably. This is important to know as the presence of macroprolactin, for example, may lead to falsely high PRL levels as measured by many assays, particularly in patients where this form of PRL accounts for significant proportions of the total circulating PRL (Fahie-Wilson & Smith 2013).

Secondly, studies investigating the relationship between PRL levels and breast cancer risk have also predominantly focused on circulating PRL levels. However, PRL functions not only in an endocrine manner, where it is secreted by the pituitary and acts on distant tissues such as the mammary gland, but also in an autocrine/paracrine [i.e., locally produced PRL from mammary (tumor) cells that acts directly on the cell itself (autocrine) or neighboring cells (paracrine)] fashion (Ben-Jonathan et al. 2002, Clevenger et al. 2003, Muthuswamy 2012). Amplification (or over-expression) of the autocrine/paracrine loop within the breast tissue has, based on several observations, been suggested to be one of the mechanisms underlying the participation of local PRL in tumorigenesis (Fernandez et al. 2010). Animal and in vitro data have shown that PRL stimulates breast cancer cell proliferation, survival and migration via binding to the cell-surface PRL receptor (Ben-Jonathan et al. 2002, Clevenger et al. 2003, Moorman et al. 2013, Oakes et al. 2008, Perks et al. 2004, Sethi et al. 2012, Wen et al. 2014). The exact mechanism whereby this occurs, however, remains

poorly understood (Tikk et al. 2015). Although the extrapituitary production of PRL may not cause detectable systemic changes in serum PRL (Chen 2015), it is nevertheless immediately available to local breast cancer cells and could be biologically very significant in terms of oncogenesis (Chen 2015, Harvey 2012, Sethi et al. 2012). Extra-pituitary PRL expression escapes negative control by dopamine. Although dopamine agonists, such as bromocriptine, are very efficient at reducing pituitary PRL levels in hyperprolactinemic patients, they are ineffective for targeting autocrine/paracrine PRL, meaning that this source of the hormone cannot be controlled by PRL-lowering drugs that act on the pituitary (Harvey 2012). Some observations (Chen 2015, Nitze et al. 2013) suggest that an autocrine/paracrine effect by PRL is unlikely to be a general mechanism promoting breast cancer cell growth and that the role of PRL as an autocrine/paracrine growth factor should be reevaluated (Chen 2015).

Thirdly, after the proposal that the PRL/PRLR pathway could play an etiological role in breast cancer, the race began to search for an effective PRLR blocker (Chen 2015). Efforts to develop a PRL receptor blocking agent (Damiano & Wasserman 2013) have failed so far, and all such drug candidates to date in monotherapy have proven to be ineffective (Chen 2015, Froes Brandao et al. 2016). Moreover, it also has been shown that PRLR expression is associated with better clinical outcome in patients with breast cancer and therefore may be more likely to play a protective and suppressive role in breast cancer rather than a promoting role (Hachim et al. 2016).

Several lines of evidence suggest that PRL can have 'protective' attributes. It has been shown that PRL can act as invasion/metastasis suppressor hormone in breast cancer (Nouhi et al. 2006). The 16kDA PRL isoform, which is a PRL fragment of the full-length 23 kDA PRL hormone, has been shown to have anti-angiogenic effects in vivo (Faupel-Badger et al. 2010b). Angiogenesis or blood vessel formation is indispensable for breast cancer development and progression and PRL can act as a stimulatory (the unmodified, full-length 23 kDA PRL hormone) or inhibitory (the proteolytic PRL fragments ranging from 14 to 18kDA, also known as vaso-inhibins) factor on growth, dilatation and remodeling of blood vessels. In its (anti)-angiogenic function PRL can act both as a circulating hormone and in an autocrine/paracrine fashion (Andres & Djonov 2010). In breast cancer, the role of PRL could depend on the production of vaso-inhibins, which can be generated from systemic PRL or from PRL produced and secreted by human breast cancer cells. Reduced levels of vaso-inhibins (due to low levels of protease activity) create a more favourable angiogenic condition for tumor progression (Clapp et al. 2008). This supports the complex role of PRL and puts forward the concept that PRL may possess a dual role in breast carcinogenesis, acting as a growth and survival factor (pro-oncogenic) as well as suppressor hormone.

Considering the possible association between antipsychotic medication, PRL, and breast cancer risk, further well conducted research is needed to assess the extent, if any, to which antipsychotics contribute to the increase of breast cancer risk in people using antipsychotics, over and above other breast cancer risk factors. Moreover, several reports describe mechanisms of cancer protection with antipsychotic medication. Recently, studies have revealed that antipsychotics, such as phenothiazines, pimozide or penfluridol, have antiproliferative activity and promote apoptosis in different types of cancer, including breast cancer (Amson et al. 2013, Gil-Ad et al. 2004, Ke et al. 2014, Lu et al. 2015, Min et al. 2014, Ranjan et al. 2016, Sachlos et al. 2012, Wiklund et al. 2010, Wu et al. 2014, Wuonola et al. 1998, Yeh et al. 2012, Zhelev et al. 2004). Thioridazine, belonging to the phenothiazine drug group, targets breast cancer and achieves a synergistic effect with other antiproliferative drugs. For example, it has been shown that co-delivery of thioridazine and doxorubicin, a highly potent and widely used chemotherapeutic agent for the treatment of various types of cancers including breast cancer, may provide a promising strategy for breast cancer treatment by targeting both cancer cells and cancer stem cells. Cancer stem cells express a high level of dopamine receptors, and the selective antiproliferative effect of thioridazine against the cancer stem cells might occur via the dopamine receptor antagonism (Ke et al. 2014). Ranjan et al. (2016) demonstrated the anti-metastatic effects of the FGA penfluridol in breast cancer models. Their results indicated that penfluridol effectively reduces the growth of primary triple-negative breast cancer tumors and especially metastatic growth in the brain. Wu et al. (2014) showed that penfluridol is not only cytotoxic to cancer cells in vitro but can also inhibit tumor growth in vivo. Dysregulation of cholesterol homeostasis by penfluridol may be involved in its anti-tumor mechanisms. Finally, it has been shown in vitro that the (PRL-elevating) phenothiazines (e.g., thioridazine and chlorpromazine) may be promising anti-hormone therapy sensitizing compounds for enhancing the effect of tamoxifen, one of the cornerstone anti-hormonal treatments for breast cancer patients, in tamoxifen-resistant human breast cancer cells (Huang et al. 2011, Yde et al. 2009). A recently conducted study demonstrated a conceivable resolution of tamoxifen-induced side effects when using the PRL-elevating SGA compound risperidone, without interfering the efficacy of tamoxifen against breast cancer in both in vitro and in vivo models (Yeh et al. 2014). If antipsychotics are used in breast cancer patients receiving anticancer therapy, drug-drug interactions always need to be checked. However, for tamoxifen, antipsychotics generally give much less interactions than antidepressant drugs which often interfere with cytochrome P450 2D6 (CYP2D6) just like tamoxifen (Desmarais & Loper 2009).

Several experts (Peveler et al. 2008, Rahman et al. 2014), as well as the product labelling of most (the exceptions being aripiprazole and clozapine) antipsychotics advise one has to be careful to use PRL-elevating antipsychotics in breast cancer patients or patients with a past history or family history of breast cancer. This advice is of course something different than the scope of this review focusing on breast cancer risk. Although certain antipsychotics (i.e., the PRL-elevating antipsychotic olanzapine) have been used effectively without safety concerns in the management of chemotherapy-induced nausea and vomiting in patients with breast cancer (Lau et al. 2016, Navari 2014, 2016), until now, no controlled studies about the effect of antipsychotics on the prognosis of women with breast cancer have been conducted. Although it must be clear that antipsychotics should not be withheld for breast cancer prevention reasons to patients in need of this sometimes life-saving medication, even if classical breast cancer risk factors are present, clinicians must weigh, as with any case, the potential benefits and risks of using these medications in patients with breast cancer. In fact, it may be more reasonable to use these drugs in breast cancer patients when there are strong clinical reasons to prescribe such medications, for example in patients where schizophrenia is life-threatening and/or very debilitating or the risk of seriously exacerbating the disease by avoiding antipsychotic treatment may outweigh the possible risk of elevated PRL levels. It is advisable that the oncologist and clinician be involved together with the patient to arrive at an informed decision.

CONCLUSIONS

After years of scientific research, the true role of PRL in breast cancer etiology remains elusive (Chen 2015). Results of prospective studies considering the effect of pituitary PRL on breast cancer risk are inconsistent and only partially agree. In studies evaluating the relationship between pituitary PRL levels and breast cancer risk factors, only the associations with nulliparity and hormone therapies (OC and HRT) have been confirmed. Until today, no causal link between (chronic) administration of antipsychotics and breast tumorigenesis in humans has been shown. Finally, antipsychotic-induced HPRL is not mentioned by the National Cancer Institute (2016) as an established factor increasing a woman's risk of breast cancer (Rahman et al. 2014). In the recently published updates of the World Federation of Societies of Biological Psychiatry (WFSBP) guidelines, breast cancer is not recognized as a potential adverse outcome of antipsychotic-induced HPRL (Hasan et al. 2013). This recommendation, together with results of studies concerning antipsychotics and breast cancer risk in women with schizophrenia, should provide some reassurance to both clinicians and their patients on the (long-term) safety of these agents.

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Johan Detraux & Marc De Hert planned the review, did the initial literature search and wrote the first draft; Brendon Stubbs, Davy Vancampfort & Tine Sabbe worked on subsequent versions of the text from a psychiatry perspective; Hans Wildiers worked on subsequent versions of the text from a breast expert perspective

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