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REVIEW ARTICLE

Hormones and gallbladder cancer in women

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Abstract

Epidemiological evidence suggests that the incidence of gallstone disease and gallbladder cancer is higher in women. We analyzed the literature on estrogen and progesterone receptor expression in gallbladder cancer in women. A systematic search was done using Medline, Embase, and Cochrane Central Register of Controlled Trials for the years 1983–2009. The search terms used included 'gallbladder', 'gallstone', 'oestrogen/estrogen', 'progesterone', 'cancer', 'cholelithiasis', 'hormone,' and 'motility'. Hormone receptor expression in gallbladder cancer was analyzed in 11 studies of which immunohistochemistry was used in 10 and enzyme immunoassay in one study. Sample sizes varied from 3 to 141. Estrogen and/or progesterone receptor expression was detectable in gallbladder cancer tissue samples in nine studies, whereas four studies failed to confirm these findings. The data on the association of hormone receptor expression to tumor differentiation is contradictory and needs further evaluation.

Keywords Breast cancer · receptor expression

Introduction

Epidemiological evidence suggests a higher incidence of gallstone disease and gallbladder cancer in women.[1–3] Attempts at investigating the association between the female sex hormones and gallbladder cancer have centered on demonstrating the expression of hormone receptors, viz. estrogen (ER) and progesterone (PR) in resected/biopsied specimens of gallbladder carcinoma.[4–15] The rationale behind this was that if hormone receptor expression could be demonstrated in gallbladder cancers, this could offer an additional therapeutic strategy in the form of anti-hormone therapy. Hormone receptor expression is routinely evaluated in breast cancer where it serves to prognosticate as well as guide treatment.[16]

Methods

A systematic *Medline* and *Embase* search was performed to identify existing literature on female sex hormones and gallbladder disease, and gallbladder cancer. The search strategy was that described by Dickersin *et al*[17] with the appropriate specific search terms for 'gallbladder', 'gallstone', 'estrogen/oestrogen', 'progesterone', 'cancer', 'cholelithiasis', 'hormone,' and/or 'motility'. All the available publications in the past 30 years were considered. No studies were excluded from the analysis.

Results

Hormone receptor expression in gallbladder cancer

Eleven studies, including an article in Spanish and one in Japanese that were translated to English, were found. Yamamoto *et al*[6] divided gall bladder cancers into metaplastic and non-metaplastic types based on the presence or absence of metaplastic changes in the tumor tissues and the surrounding mucosa. They found a link between ER immunoreactivity and metaplastic tumors.[7] Subsequent reports conflictingly show either over-expression or loss of expression of hormone receptors in gallbladder cancer tissue. Table 1 summarizes these studies.[4,5,7–15]

Nakamura *et al*[5] evaluated 21 patients with gallbladder cancer (9 well-differentiated, 8 moderately differentiated, 2

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Table 1 Studies examining hormone receptor expression in gallbladder cancer

First author and year of study	Number of patients	Hormone receptor studied	Technique/criteria for labelling positive**	Percent positive for ER/PR	Associations noted with differentiation of tumor	Percent of patients with gallstones	Conclusions
Nakamura 1989[5]	21	ER + PR	IHC	Receptor expression in nucleus: ER – 52.4% PR – 0% in cytoplasm ER – 28.6% PR – 66.7%	ER (nuclear and cytoplasmic) and PR (cytoplasmic) localization Well differentiated (n=9) 44.4 and 66.7% Mod. well differentiated (n=8) 50 and 50% Poorly differentiated (n=2) 100 and 100%	NA	Higher tendency of moderately- and poorly-differentiated adenocarcinoma to have an ER-positive rate than well-differentiated adenocarcinoma
Yamamoto 1990[7]	114	ER	IHC Positivity – immunoreactivity confined to nucleus of epithelial cell	Receptor expression in nucleus: ER – 22.8%	ER (nuclear) localization Well differentiated (n=75) 29.3% Mod. well differentiated (n=21) 9.5% Poorly differentiated (n=17) 11.8%	NA	Presence of ER is related to metaplasia of the gallbladder mucosa; ER immunoreactivity more frequent in well differentiated cancers
Ko 1995[8]	22	ER	IHC	Receptor expression in nucleus: ER – 12% (weak)	Data reported as no correlation but not illustrated	NA	Weak estrogen receptor staining occurs in a very small percentage of gallbladder carcinomas
Malik 1998[9]	30	ER	IHC	Receptor expression in cytoplasm: ER – 60%	ER (cytoplasmic) localization Well differentiated (n=4) 75% Mod. well differentiated (n=19) 68% Poorly differentiated (n=7) 28%	80%	Poor differentiation more likely to be associated with negative ER expression
Sumi 2004[10]	26	ERα + ER β isoforms	IHC Positive for ERα - >10% of nucleus of cells stained Positive for ERβ - >40% of nucleus stained	Receptor expression in nucleus: ERβ – 38-42%	ER (nuclear) localization Papillary and well differentiated (n=15) 60% Mod. well differentiated (n=11) 9%	NA	Lack of expression of Erβ isoform at invasive front of tumour associated with more aggressive malignancy
Baskaran 2005[11]	21	ER + PR	EIA/values <1.7fmol/mg cytosol protein were	Receptor expression in cytosolic extracts: ER – 43%	NA	NA	ER expression no different in benign or malignant tissue, while PR expression greater in

(*contd...*)

Table 1 (*contd...*)

First author and year of study	Number of patients	Hormone receptor studied	Technique/criteria for labelling positive**	Percent positive for ER/PR	Associations noted with differentiation of tumor	Percent of patients with gallstones	Conclusions
			considered negative for receptor expression	PR – 72%			malignant tissue
Shukla 2007[4]	62	ER + PR	IHC Positive - >5% of cells showing nuclear staining	Receptor expression in nucleus: ER – 0% PR – 2%	NA	90%	Intense metaplasia and poor differentiation – less likely to have hormone receptor expression
Park 2008[12]	30	ERα + ERβ isoforms + PR	IHC / >10% of total cells from the tissue sample were stained	Receptor expression in nucleus: ERα – 0% PR – 0% ERβ – 73.3%	ERβ (nuclear) localization Well differentiated (n=13) 77% Mod. well differentiated (n=13) 85% Poorly differentiated (n=4) 25%	NA	ER β positivity correlated with tumour differentiation; all specimens were negative for ERα + PR
Ohnami 1988[13]	3	ER	IHC and DCC	Receptor expression in nucleus: ER – 33%	NA	NA	ER expression by DCC in 1 patient
Roa 1995[14]	141	p29 ER associated protein and pS2 estrogen induced protein	IHC Stratified according to tissue cells stained into: + - <5% ++ - 5-30% +++ - >30%	ER-associated protein expression in cytoplasm: p29 – 40% pS2 – 38%	NA	NA	ER associated/induced proteins are expressed in most gallbladder cancer samples
Albores-Saavedra 2008[15]	7	ER / PR	IHC	Receptor expression: ER – 0% PR – 0%	NA	71%	Cribriform cancer of gallbladder lack ER/PR expression

ER, estrogen receptor; PR, progesterone receptor; IHC, immunohistochemistry; EIA, enzyme Immunoassay; NA, not available; DCC, dextran coated charcoal
**Cut-off values for receptor expression have not been mentioned in the Table if the data was not available from the manuscript

poorly differentiated, 1 poorly differentiated with squamous metaplasia, and 1 carcinosarcoma), and used breast cancer specimens as controls. They reported a higher ER expression in tumors that exhibited metaplasia, and that ER immunoreactivity in nucleus and the cytoplasm increased as the degree of differentiation decreased. They did not find PR immunoreactivity in the nucleus of any of the 21 specimens.

Yamamoto *et al*[7] described hormone receptor expression studies in 189 gallbladder tissue samples including 114 cancer specimens with the rest being benign pathologies. They found no ER immunoreactivity in their specimens of normal gallbladder. In their cancer specimens, they found that ER immunoreactivity was more frequent in patients with well-differentiated tumors (29.3%) than in those with poorer differentiation (9.5–11.8%). They also found a higher incidence of hormone receptor immunoreactivity in metaplastic tumor tissue as opposed to non-metaplastic tissue. The incidence of cholelithiasis specifically in the cancer specimens was not mentioned.

Malik *et al*[9] studied tumor tissue from 30 patients with gallbladder cancer. Gallstones were present in 80% of patients. Using immunohistochemistry, they found a trend toward loss of hormone receptor expression in poorly differentiated tumors. Sumi *et al*[10] studied 26 samples of gallbladder cancer which included 15 patients with papillary and well-differentiated tumors and 11 with moderately differentiated tumors. They reported a loss of estrogen receptor expression at the invasive front in cancers that had more aggressive characteristics.

We studied ER/PR expression in 62 specimens of gallbladder cancer; 90% patients had moderately to poorly differentiated adenocarcinomas.[4] Gallstones were present in 90% of our patients. We found no expression of estrogen receptors in any samples, and progesterone receptor was positive in only one patient. This was in contrast to another study from India.[11] Using enzyme immunoassay, Baskaran *et al*[11] found that estrogen receptor expression was not different between benign and malignant tissue but there was a higher expression of progesterone receptors in malignant tissue samples.

Park *et al*[12] using immunohistochemistry to study isoforms of ER, viz α and β, and PR, too found a loss of ER α and PR expression in poorly differentiated tumors. However, they did find ER β expression which correlated with 3- and 5-year survival. Roa *et al*[14] examined protein expression in primary and metastatic gallbladder carcinoma and using immunohistochemistry. They concluded that ER associated or induced protein expression was higher in advanced tumors or metastasis; this could possibly have been because of the varied sizes in the three cohorts described by them, viz. early, advanced and metastatic disease. Their study cohort included 21 patients with early cancer, 90 patients with advanced (possibly locally) cancer, and 30 patients with metastatic cancer.

Discussion

Both ER and PR studies are an important part of the pathological examination of breast cancer specimens. McGuire *et al*[18] demonstrated that binding of a cytosol estrogen receptor led to the translocation and binding of a nuclear estrogen receptor which then led to the induction of the progesterone receptor. This prompted them to infer that rather than measuring ER, it was the expression of PR that was more an indication of a functionally intact receptor system and thus a more accurate indicator of endocrine responsiveness. In the present review of literature, while some studies have reported the presence of estrogen receptor[5,7–10,12–14] or progesterone receptor expression[11] or both, other studies have failed to confirm this expression of hormone receptors in tumor tissue.[4,8,12,15]

Using the pathogenetic algorithm put forth by Wistuba and Gazdar,[19] we postulated that tumor metaplasia secondary to gallstone disease could result in the loss of hormone receptor expression and that non-metaplastic tumors that are more commonly encountered in patients with anomalous pancreatic-bile duct junction (APBDJ) anomalies were possibly the ones with increased hormone receptor expression.[4] This could explain the higher incidence of hormone receptor expression in tumors in studies from Japan and China where APBDJ is a more common cause of gallbladder cancer as compared to the Western world.[20]

Some studies have reported a loss of hormone receptor expression with poorer differentiation,[4,7,9,10,12] while others have suggested quite the contrary.[5] It is likely that even normal expression of ER and PR can mediate hormone effects on tumor cells. Absence in poorly differentiated cells indicates that the cells have escaped hormonal control leading to altered tumor biology.

An interesting finding in the study from India[21] is the fact that ER and PR expression even in breast cancer tumor samples have been reported to be lower than reported in Western literature. The cause for this in breast cancer[21] has been attributed to younger patient age as well as higher grades of cancers–which reflects the nature of the disease entity in gallbladder cancer in India, as well.

Conclusion

The contradictory evidence concerning hormone receptor expression in gallbladder carcinoma suggests that a direct role for female sex hormones in genesis of gallbladder cancer in women is not yet established.

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