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Urban–rural differences in breast cancer incidence by hormone receptor status across 6 years in Egypt

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Abstract Breast cancer incidence is higher in developed countries with higher rates of estrogen receptor positive (ER+) tumors. ER+ tumors are caused by estrogenic exposures although known exposures explain approximately 50% of breast cancer risk. Unknown risk factors causing high breast cancer incidence exist that are estrogenic and development-related. Xenoestrogens are such risk factors but are difficult to study since developed countries lack unexposed populations. Developing countries have urban–rural populations with differential exposure to xenoestrogens. This study assessed urban–rural breast cancer incidence classified by hormone receptor status using data from Gharbiah population-based cancer registry in Egypt from 2001 to 2006. Urban ER+ incidence rate (per 100,000 women) was 2–4 times (IRR = 3.36, 95% CI = 4.84, 2.34) higher than rural incidence rate. ER− incidence rate was 2–3 times (IRR = 1.86, 95% CI = 2.38, 1.45) higher in urban areas than in rural areas. Our findings indicate that urban women may probably have a higher exposure to xenoestrogens.

Keywords Breast cancer incidence · Hormone receptor status · Mammary stem cells · Xenoestrogens · Egypt

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Introduction

Breast cancer incidence differs across various populations with higher incidence rates in developed countries [1]. However, breast cancer is not a homogeneous disease and there are various subtypes of this malignancy. One of the important ways of dividing breast cancer into subtypes is by using hormone receptor status (HRS) [2]. The need to develop these subtypes of breast cancer arose due to their differential response to different modes of therapy [3]. Presence of estrogen receptors (ERs) and progesterone receptors (PRs) or ER+/PR+ or hormone receptor positive (HR +) breast cancer, implies the best response to anti-estrogen therapy whereas absence of these receptors or ER−/PR− or hormone receptor negative (HR−) breast cancer, implies poor response to anti-estrogen therapy. These differences are more pronounced if we take into account only the ER status of tumors [3]. The natural history of disease between ER+ and ER− tumors also varies with better prognosis overall for ER+ patients and

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with different sites and time periods of relapse [4]. Epidemiological analysis of breast cancer by HRS shows distinct patterns for ER+ and ER− cancers. Risk factor distribution differs among patients based on HRS with reproductive factors that increase a woman's lifetime exposure to endogenous estrogens resulting in ER+ cancer [5, 6]. Other risk factors such as genetic risks, radiation, and smoking give rise to ER− cancers [5, 7]. Overall, these differences imply that ER+ and ER− cancers denote different subtypes of breast cancer with different risk factors, clinical pictures, and outcomes [3].

Another characteristic difference of ER+ and ER− tumors is the close correlation of ER+ incidence with populations having high breast cancer incidence. Studies involving the Surveillance Epidemiology and End Results (SEER) show ER+ cancers to be more frequent after menopause [8, 9] and more common among Caucasians than other races [10–12]. In addition, international studies have clearly indicated that ER+ breast cancer is higher in developed countries [13]. To add to these population trends Li et al. [14] have shown that most of the increase in breast cancer incidence in US has been due to an increase in ER+ breast cancer.

Thus, existing evidence suggests that ER+ cancer is high and increasing in the industrialized parts of the world mainly due to risk factors that are estrogenic in nature. However, most of the hereditary and environmental risk factors of breast cancer explain only up to 50% of breast cancer risk [15, 16]. This implies that other unknown estrogenic risk factors increase the risk of breast cancer, mostly later in life. Such estrogenic risk factors related to industrial development are a diverse group of chemicals called xenoestrogens. These xenoestrogens include chemicals in plastics such as bisphenol-A (BPA), phthalates and polyvinyl chloride (PVC), pesticides and insecticides like DDTs, polychlorinated biphenyls (PCBs), parabens and placental extracts in cosmetics, aromatic amines, industrial solvents like benzene and toluene, and air pollutants such as polyaromatic hydrocarbons (PAHs) [17]. It is apparent xenoestrogens pervade almost all areas of modern life in developed parts of the world [17].

There is increasing evidence that xenoestrogens are related to breast cancer [17, 18] and primarily cause ER+ breast cancer [19–21]. However, studies in humans have been inconclusive and an important reason has been the lack of comparison between populations differentially exposed to xenoestrogens since in developed countries exposure to xenoestrogens seems widespread [22]. Studies examining xenoestrogens in the blood and urine of individuals in US and other developed countries have found that more than 90% of the population had been exposed to xenoestrogens [23–25]. However, populations differentially exposed to xenoestrogens are available in developing countries e.g., in urban and rural areas. Numerous studies from various countries have shown higher presence and exposure to xenoestrogens in urban areas [26–30]. Since urban populations are more exposed to xenoestrogens, we hypothesize that they have higher incidence of breast cancer and ER+ cancer compared with rural areas. We have recently published these hypotheses [31] and have already shown that incidence of breast cancer is indeed higher in urban areas than rural areas in Egypt [unpublished data]. The purpose of this study was to investigate the urban–rural differences in HRS-specific breast cancer incidence in the same population as the previous study.

Materials and methods

Study population

The study population consisted of women diagnosed with primary breast cancer with known ER or PR status for a period of 6 years (2001–2006), from the Gharbiah population-based cancer registry, Tanta, Egypt. Overall, we considered 3,673 cases for our study but had to exclude cases with missing ER and PR information from the respective analyses. ER and PR information was not routinely entered in the registry database especially for the years 2001–2004. Therefore, for all cases lacking this information, medical records were obtained from Tanta Cancer Center (TCC), Gharbiah Cancer Registry (GCS) and any other centers for which medical records were available. Cases' registry number, age at diagnosis, address, address code, smoking status, occupation, basis of diagnosis, estrogen receptor status, progesterone receptor status, tumor grade, stage, morphology, medical record number, and place of reference were abstracted from the routinely collected registry data. Use of human subject data was approved by the University of Michigan Institutional Review Board and the Gharbiah Cancer Center Ethics Committee.

Gharbiah population-based cancer registry

The Gharbiah population-based cancer registry was founded in 1998 as a part of the Middle East Cancer Consortium (MECC) [32]. As an active registry, it collects cases from a number of sources in the province. Most of the breast cancer cases came from TCC (40–50%), GCS (10–12%) and Tanta University Hospital (10–12%). Following abstraction of data, it is entered on the International Agency for Research on Cancer (IARC) software CanReg4. Registry staff was trained in data extraction and entry, and is periodically monitored by site visits from the

faculty of Emory School of Public Health, IARC, and the MECC registry Steering Committee members.

Most of the cases (95.8%) were diagnosed by pathological confirmation [33]. The World Health Organization (WHO) ICD-02 coding was used to determine the types of cancer in 1999 and 2000 after which ICD-03 coding was used. Cases were registered with SEER staging information from 1999 to 2002 and the American Joint Committee on Cancer (AJCC) staging was begun in the registry only from 2003, although records for patients were retrieved and all previous SEER staging was replaced by AJCC staging by determining the TNM status of breast cancer for these patients.

ER and PR determination

ER and PR status was determined by immunohistochemistry (IHC) in all the centers providing cases to the registry. Paraffin sections of tissues are boiled in 10 mM citrate buffer for 10–20 min followed by cooling at room temperature for 20 min. Monoclonal antibodies for ER and PR are then added to separate tissue sections and incubated for 30 min followed by visualization. The percentage of stained cells and strength of staining determines the score of positivity for ER and PR (1 +, 2 + or 3 +) with presence of stain in <1% cells or weak staining implying receptor negative status [34]. For our analyses, we dichotomized the HRS into either positive or negative.

Gharbiah province

Gharbiah province is an administrative region located 90 km north of Cairo in the Nile Delta Region. It has eight districts each with a capital city with Tanta being the capital of Tanta district as well as of the entire province. Gharbiah has a population of more than four million people and 49% of them are women. Approximately, 30% of the population resides in urban areas and almost 47% of the female population are below the age of 20 according to the 2006 Central Agency for Public Mobilization and Statistics (CAPMAS) census.

Census data

Census data for female population in Gharbiah were obtained from the 1996 and 2006 CAPMAS [35] census and constant growth of the population was assumed to predict population estimates for the years in-between using a linear regression model. The linear growth rates of eight districts were applied to the urban and rural populations within those districts to determine urban and rural populations from 1999 through 2006. The census data consisted of 16 age categories at 5-year intervals. Six age categories were created from these by collapsing the age categories below 29 years followed by 10-year intervals. These population figures formed the denominators to calculate the overall, age-specific, and urban–rural incidence rates for breast cancer in women.

Urban–rural classification

The urban–rural classification followed the CAPMAS coding of urban and rural areas [35]. Urban areas consisted of all the capital cities of the eight districts of the province while the villages surrounding the capital cities and villages in rest of the district were considered rural. Each case in the registry is assigned a residence code based on their residential address that follows the CAPMAS coding. This code was used to classify patients as urban or rural.

Statistical analyses

Descriptive statistics and incidence rate analyses were completed using SAS (Version 9; SAS Institute, Cary, NC). Yearly crude and age adjusted incidence rates for breast cancer were calculated for Gharbiah province and six age categories classified by urban and rural areas for the province and each age category. The six age categories were 0–29, 30–39, 40–49, 50–59, 60–69, and 70 or more. We stratified our analyses by HRS, specifically assessing separately, the rates of ER+, ER−, PR+, PR−, ER+/PR+, ER+/PR−, ER−/PR+, and ER−/PR− tumors. Women with ER or PR status that were unknown or could not be assessed were excluded from the analyses. We computed the proportion of women with a particular HRS (among those with known hormone status) by year of incidence, age group, and urban–rural status. We then calculated urban–rural incidence, and incidence rate ratios (IRRs) and 95% confidence intervals (CI) using negative binomial regression. We considered age, stage, and year of diagnosis as potential confounders in our analysis. We also evaluated how the incidence of a given HRS changed over time using *P*-values for trends.

Results

Among the 3,673 cases which were a part of this study, 61.83% were urban (Table 1). Most of the cases presented at Stage II (26.9%) or Stage III (33.24%). Most of these cases had been diagnosed microscopically (histology of the primary—77.14% or FNAC—17.25%).

ER status was known for 47.63% of cases and PR status was known for 37.19% of cases overall (Table 2). The proportion and incidence of cases with unknown ER and

Table 1 Characteristics of breast cancer cases in Gharbiah, Egypt, 2001–2006

Variable	Descriptive category	Urban no. (%)	Rural no. (%)	Overall no. (%)
Total cases		2,271 (61.83)	1,402 (38.17)	3,673 (100)
Year of diagnosis	2001	378 (65.51)	199 (34.49)	577 (15.71)
	2002	431 (69.40)	190 (30.60)	621 (16.91)
	2003	349 (58.17)	251 (41.83)	600 (16.34)
	2004	388 (60.44)	254 (39.56)	642 (17.48)
	2005	347 (59.22)	239 (37.71)	586 (15.95)
	2006	378 (58.42)	269 (37.71)	647 (17.62)
Age-groups	0–24	10 (52.63)	9 (47.37)	19 (0.52)
	25–29	36 (52.94)	32 (47.06)	68 (1.85)
	30–34	111 (57.81)	81 (42.19)	192 (5.23)
	35–39	195 (53.72)	168 (46.28)	363 (9.88)
	40–44	335 (58.88)	234 (41.13)	569 (15.49)
	45–49	397 (63.72)	226 (36.28)	623 (16.96)
	50–54	409 (65.02)	220 (34.98)	629 (17.13)
	55–59	277 (61.83)	171 (38.17)	448 (12.20)
	60–64	217 (64.78)	118 (35.22)	335 (9.12)
	65–59	135 (67.84)	64 (32.16)	199 (5.42)
	70+	139 (63.76)	79 (36.24)	218 (5.94)
Stage*	I	75 (63.56)	43 (36.44)	118 (3.21)
	II	586 (59.31)	402 (40.69)	988 (26.90)
	III	713 (58.40)	508 (41.61)	1,221 (33.24)
	IV	192 (49.74)	194 (50.26)	386 (10.51)
Basis of diagnosis†	Histology	1,560 (60.56)	1,016 (39.44)	2,576 (77.14)
	FNAC	331 (65.81)	172 (34.19)	503 (17.25)
	Others	76 (66.09)	39 (33.91)	115 (5.61)

*26.14% of cases had missing or unknown AJCC stage information

† 13.04% of cases had missing information on basis of diagnosis

PR status were almost similar for all years. Among all cases, overall 32.82% were ER+, and 14.82% were ER−. Among all cases, overall 21.55% were PR+ and 15.62% were PR−. The average incidence of ER+ cancer was the highest (10.92 per 100,000 women) followed by PR+ cancer (7.18 per 100,000 women), PR− cancer (5.18 per 100,000 women), and ER− cancer (4.93 per 100,000 women) (Table 2). Distribution of cases by joint HRS shows that overall ER+/PR+ cancer had the highest incidence (6.44 per 100,000 women) followed by ER−/PR− cancer (3.74 per 100,000 women). The incidence of ER+/PR− cancer was low (1.44 per 100,000 women) followed by the lowest incidence of ER−/PR+ cancer (0.73 per 100,000 women) (Table 3). The proportion (average—62.89%) and incidence (average—20.88 per 100,000 women) of cases with unknown ER/PR status remained almost constant throughout the years. We did not see any noticeable trends in the incidence of breast cancer by HRS as shown by *P*-values for trend.

Urban distribution of HRS shows that ER+ incidence was the highest followed by PR+ positive incidence within both urban and rural areas (Table 4). ER− and PR− rates were quite similar within both urban and rural areas. On comparison of urban and rural incidences, ER+ incidence in urban areas was 2–4 times higher than ER+ incidence in rural areas (overall IRR = 3.36, 95% CI = 2.34, 4.84) (Table 4). Following this PR+ incidence was 2–4 times higher in urban areas than in rural areas (overall IRR = 2.29, 95% CI = 1.70, 3.70). ER− (overall IRR = 1.86, 95% CI = 1.45, 2.38) and PR− (overall IRR = 1.89, 95% CI = 1.60, 2.24) (Table 4) incidence were almost 2–3 times higher in urban than in rural areas.

Urban–rural distribution of joint HRS showed that ER+/PR+ cancer incidence in urban areas was highest, being 2–4 times that in rural areas (overall IRR = 2.33, 95% CI = 1.68, 3.23) (Table 4). ER−/PR− cancer was also 1–3 times higher in urban areas than rural areas (2,001 overall IRR = 1.72, 95% CI = 1.28, 2.32) (Table 5). ER+/PR− and ER−/PR+ cases were very few and therefore they were not included in further analysis in Table 5.

Age-specific distribution of breast cancer incidence by HRS showed higher incidence for all receptors in urban areas when compared with rural areas (Table 4) (Fig. 1). Within urban areas ER+ incidence was the highest in all age-groups followed by PR+ incidence. ER− and PR−

Table 2 Distribution of number, percentage and overall incidence* of breast cancer by hormone receptor status in Gharbiah, 2001–2006

Year	ER+			ER−			ER unknown			PR+			PR−			PR unknown		
	No.	%	Inc*	No.	%	Inc*	No.	%	Inc*	No.	%	Inc*	No.	%	Inc	No.	%	Inc*
2001	188	32.58	10.37	68	11.79	3.75	321	55.63	17.70	111	19.24	6.12	98	16.98	5.40	368	63.78	20.29
2002	172	27.70	9.33	92	14.81	4.99	357	57.49	19.36	98	15.78	5.31	99	15.94	5.37	424	68.28	22.99
2003	187	31.17	10.19	100	16.67	5.45	313	52.17	17.06	130	21.67	7.09	109	18.17	5.94	361	60.17	19.68
2004	192	29.45	10.26	91	13.96	4.86	369	56.60	19.71	120	18.41	6.41	86	13.19	4.59	446	68.41	23.83
2005	180	30.72	9.77	86	14.68	4.67	320	54.61	17.37	121	20.65	6.57	81	13.82	4.40	384	65.53	20.84
2006	293	45.29	15.62	110	17.00	5.86	244	37.71	13.01	217	33.54	11.57	101	15.61	5.38	328	50.70	17.49
Overall	1212	32.82	10.92	547	14.82	4.93	1,924	52.37	17.37	797	21.55	7.18	574	15.62	5.18	2,311	62.81	20.85
P for trend†			0.93			0.91			0.95			0.98			0.99			0.91

*All incidences are per 100,000 women

† Adjusted for stage and year of diagnosis

Table 3 Distribution of number, percentage and overall incidence* of breast cancer by joint hormone receptor status in Gharbiah, 2001–2006

Year	ER+/PR+			ER+/PR−			ER−/PR+			ER−/PR−			ER/PR unknown		
	No.	%	Incidence*	No.	%	Incidence*	No.	%	Incidence*	No.	%	Incidence*	No.	%	Incidence*
2001	105	18.20	5.79	39	6.76	2.15	6	1.04	0.33	58	10.52	3.20	369	63.95	20.34
2002	86	13.85	4.66	27	4.35	1.46	12	1.93	0.65	72	11.59	3.90	424	68.28	22.99
2003	118	19.67	6.43	27	4.50	1.47	12	2.00	0.65	82	13.67	4.47	361	60.17	19.68
2004	111	17.03	5.93	14	2.15	0.75	9	1.38	0.48	72	11.04	3.85	446	68.41	23.83
2005	105	17.92	5.70	16	2.73	0.87	16	2.73	0.87	65	11.09	3.53	384	65.53	20.84
2006	190	29.37	10.13	36	5.56	1.92	26	4.02	1.39	65	10.05	3.47	330	51.01	17.59
Overall	715	19.34	6.44	159	4.34	1.44	81	2.18	0.73	414	11.25	3.74	2,314	62.89	20.88
P for trend†			0.98			0.87			0.98			0.97			0.91

*All incidences are per 100,000 women

† Adjusted for stage and year of diagnosis

cancer incidence was almost similar. Within rural areas, the incidence of all four receptor types was almost similar with slightly higher incidence for ER+ and PR+ in 2006. Comparison of urban–rural incidences showed that the incidence of all HRS was higher in urban areas than rural areas for all age-groups with the urban incidence of ER+ cancer being the highest in all age-groups (Table 4). Age-specific distribution of breast cancer incidence by joint HRS showed that ER+/PR+ cancer incidence was the highest in urban areas (Table 5) (Fig. 2) in most age-groups. Within rural areas, ER+/PR+ and ER−/PR− cancer incidence was almost similar except in 2006.

Discussion

This is the first study, from a population-based cancer registry in a developing country, to show a higher incidence rate of ER+ breast cancer in urban areas compared with rural areas. This study confirms earlier findings that populations with higher breast cancer incidence also demonstrate higher ER+ incidence. This pattern is visible both in comparison of HRS incidence and age-specific incidence classified by HRS. The reasons for higher incidence of ER+ cancer in urban areas are multi-factorial. It is quite possible that women in urban areas have better nutrition and development which leads to early menarche. They might be more educated resulting in higher age of marriage, lesser number of children, and reduced breastfeeding [36]. All of these reproductive factors result in higher lifetime exposure of women to endogenous estrogens and thus can increase ER+ cancer. Although in the context of Egypt, we found that the urban–rural differences among women in terms of nutritional status, age of first childbirth, and amount of breastfeeding were minimal as indicated by the Egyptian Demographic Health Survey [37].

In addition, we have also shown in our recent study that breast cancer incidence is 3–4 times higher in urban areas of Egypt and this cannot be explained by known reproductive risk factors [unpublished data], a fact that has also been seen

Table 4 Urban–rural incidence rates* and incidence ratios of breast cancer by ER/PR status, by age-groups and overall in Gharbiah, 2001–2006

Years	Urban–rural incidence and incidence ratios								
	Age-groups (Years)								
	0–29			30–39			40–49		
	Urban	Rural	Urban–rural IRR (95% CI)	Urban	Rural	Urban–rural IRR (95% CI)	Urban	Rural	Urban–rural IRR (95% CI)
ER+									
2001	0.59	0.12	4.80 (0.44, 52.99)	22.4	5.85	3.80 (1.77, 8.17)	59.17	17.76	3.33 (1.96, 5.65)
2002	0.58	0.24	2.40 (0.34, 17.05)	21.91	5.76	3.80 (1.77, 8.17)	50.99	10.83	4.71 (2.49, 8.90)
2003	1.15	0.24	4.80 (0.88, 26.23)	16.99	7.36	2.31 (1.10, 4.85)	54.40	17.19	3.16 (1.86, 5.39)
2004	0.00	0.23	0.00	12.23	8.34	1.47 (0.67, 3.19)	66.05	16.07	4.11 (2.44, 6.94)
2005	0.88	0.12	7.21 (0.75, 69.29)	23.05	1.73	13.33 (3.96, 44.87)	42.24	19.15	2.21 (1.28, 3.81)
2006	0.86	0.24	3.60 (0.60, 21.57)	22.64	10.75	2.11 (1.12, 3.94)	87.26	40.08	2.18 (1.49, 3.17)
ER−									
2001	0.59	0.12	4.80 (0.44, 52.99)	5.85	3.51	1.67 (0.51, 5.46)	19.23	15.23	1.26 (0.62, 2.58)
2002	0.58	0.36	1.60 (0.27, 9.58)	12.68	7.49	1.69 (0.76, 3.78)	20.39	7.50	2.72 (1.18, 6.29)
2003	0.57	0.12	4.80 (0.44, 52.99)	10.20	7.36	1.38 (0.59, 3.24)	20.04	14.73	1.36 (0.68, 2.73)
2004	0.28	0.35	0.80 (0.08, 7.70)	8.90	4.45	2.00 (0.75, 5.33)	25.30	13.66	1.85 (0.95, 3.59)
2005	0.29	0.12	2.40 (0.15, 38.41)	6.92	2.88	2.40 (0.73, 7.86)	20.39	10.83	1.88 (0.89, 4.01)
2006	0.57	0.00	–	4.53	3.40	1.33 (0.38, 4.73)	32.90	15.54	2.12 (1.15, 3.89)
PR+									
2001	0.00	0.12	0.00	16.39	3.51	4.67 (1.79, 12.14)	28.11	11.00	2.56 (1.26, 5.18)
2002	0.29	0.24	1.20 (0.11, 13.25)	11.53	2.31	5.00 (1.57, 15.94)	30.59	8.33	3.67 (1.73, 7.80)
2003	0.86	0.12	7.21 (0.75, 69.29)	12.46	6.80	1.83 (0.81, 4.16)	38.65	13.10	2.95 (1.59, 5.48)
2004	0.00	0.23	–	8.90	5.00	1.78 (0.69, 4.61)	44.97	10.45	4.31 (2.26, 8.20)
2005	0.58	0.12	4.80 (0.44, 52.99)	13.83	0.58	24.00 (3.12, 184.59)	24.76	14.16	1.75 (0.89, 3.43)
2006	0.86	0.24	3.60 (0.60, 21.57)	13.59	7.92	1.71 (0.79, 3.71)	68.66	26.99	2.54 (1.63, 3.96)
PR−									
2001	0.89	0.12	7.21 (0.75, 69.29)	5.85	5.85	1.00 (0.34, 2.93)	28.11	18.61	1.51 (0.82, 2.79)
2002	0.58	0.36	1.60 (0.27, 9.58)	11.53	8.07	1.43 (0.63, 3.22)	17.48	7.50	2.33 (0.98, 5.53)
2003	0.57	0.24	2.40 (0.34, 17.05)	9.06	7.36	1.23 (0.51, 2.97)	20.04	13.91	1.44 (0.71, 2.92)
2004	0.28	0.35	0.80 (0.08, 7.70)	6.67	5.00	1.33 (0.47, 3.75)	25.30	15.27	1.66 (0.87, 3.16)
2005	0.29	0.12	2.40 (0.15, 38.41)	5.76	2.88	2.00 (0.58, 6.91)	13.11	11.66	1.12 (0.49, 2.60)
2006	0.00	0.00	–	9.06	3.40	2.67 (0.93, 7.69)	30.04	16.36	1.84 (1.00, 3.39)

Table 4 continued

Years	Urban–rural incidence and incidence ratios									Overall		
	Age-groups (years)											
	50–59			60–69			70+					
	Urban	Rural	Urban–rural IRR (95% CI)	Urban	Rural	Urban–rural IRR (95% CI)	Urban	Rural	Urban–rural IRR (95% CI)	Urban	Rural	Urban–rural IRR (95% CI)
ER+												
2001	101.55	33.33	3.05 (1.83, 5.08)	60.75	15.47	3.93 (1.67, 9.26)	72.10	7.51	9.60 (2.04, 45.19)	19.88	5.56	3.58 (2.65, 4.82)
2002	97.36	21.88	4.45 (2.48, 8.00)	63.81	24.75	2.58 (1.24, 5.36)	44.37	14.80	3.00 (0.81, 11.17)	18.24	4.77	3.83 (2.79, 5.25)
2003	108.6	24.19	4.49 (2.58, 7.80)	74.46	16.84	4.42 (2.00, 9.78)	34.88	3.64	9.60 (1.07, 85.85)	18.83	5.19	3.63 (2.68, 4.91)
2004	114.24	26.39	4.33 (2.56, 7.33)	76.95	11.02	6.98 (2.80, 17.39)	25.68	10.71	2.40 (0.48, 11.89)	19.00	5.21	3.65 (2.71, 4.91)
2005	110.49	27.34	4.04 (2.37, 6.88)	83.73	9.52	8.80 (3.32, 23.33)	53.23	25.89	2.06 (0.69, 6.12)	19.46	4.87	4.00 (2.93, 5.46)
2006	139.54	47.00	2.97 (1.94, 4.54)	74.41	31.78	2.34 (1.22, 4.50)	61.00	25.43	2.40 (0.84, 6.84)	25.69	10.49	2.45 (1.94, 3.08)
Overall IRR† and *P* for trend†										0.99	0.92	3.36 (2.34, 4.84)
ER−												
2001	21.28	11.11	1.92 (0.72, 5.13)	16.20	1.93	8.38 (0.94, 74.97)	9.01	3.76	2.40 (0.15, 38.36)	5.38	2.95	1.82 (1.13, 2.93)
2002	42.10	16.41	2.57 (1.21, 5.42)	7.98	11.42	0.70 (0.14, 3.46)	26.62	3.70	7.20 (0.75, 69.19)	7.68	3.62	2.12 (1.41, 3.20)
2003	31.03	21.50	1.44 (0.68, 3.05)	27.43	13.09	2.09 (0.73, 5.97)	8.72	0.00	–	6.89	4.46	1.55 (1.04, 2.29)
2004	22.85	9.24	2.47 (0.92, 6.64)	34.63	12.86	2.69 (1.00, 7.23)	0.00	10.71	–	6.94	3.55	1.95 (1.29, 2.95)
2005	21.05	16.41	1.28 (0.52, 3.14)	39.87	13.32	2.99 (1.14, 7.86)	53.23	11.10	4.80 (1.20, 19.19)	7.24	3.38	2.14 (1.40, 3.27)
2006	59.43	13.43	4.43 (2.11, 9.30)	47.00	13.09	3.59 (1.41, 9.12)	26.14	3.63	7.20 (0.75, 69.19)	10.49	3.50	3.00 (2.05, 4.40)
Overall IRR† and *P* for trend†										0.83	0.86	1.86 (1.45, 2.38)
PR+												
2001	64.14	19.44	3.30 (1.71, 6.38)	40.50	5.80	6.98 (1.92, 25.37)	45.06	7.51	6.00(1.16, 30.91)	11.73	3.28	3.57 (2.42, 5.27)
2002	47.37	16.41	2.89 (1.39, 5.99)	23.93	17.13	1.40 (0.50, 3.92)	17.75	11.10	1.60 (0.27, 9.57)	9.28	3.29	2.82 (1.89, 4.22)
2003	64.64	18.81	3.44 (1.79, 6.61)	43.11	13.09	3.29 (1.28, 8.49)	17.44	3.64	4.80 (0.44, 52.91)	12.09	4.13	2.93 (2.06, 4.16)
2004	58.39	19.79	2.95 (1.54, 5.65)	38.47	7.35	5.24 (1.64, 16.70)	8.56	10.71	0.80 (0.08, 7.69)	11.16	3.63	3.07 (2.13, 4.44)
2005	60.51	16.41	3.69 (1.84, 7.41)	63.79	11.42	5.59 (2.19, 14.28)	62.11	25.89	2.40 (0.84, 6.84)	12.38	3.63	3.41 (2.36, 4.94)
2006	116.28	30.89	3.76 (2.28, 6.22)	54.83	24.30	2.26 (1.06, 4.80)	52.29	14.53	3.60 (1.02, 12.75)	20.05	7.24	2.77 (2.11, 3.63)
Overall IRR† and *P* for trend†										0.97	0.99	2.29 (1.70, 3.70)
PR−												
2001	32.07	15.28	2.10 (0.93, 4.76)	32.40	7.73	4.19 (1.26, 13.91)	18.02	3.76	4.80 (0.44, 52.92)	7.98	4.13	1.93 (1.30, 2.87)
2002	52.63	17.78	2.96 (1.47, 5.95)	19.94	13.33	1.50 (0.47, 4.71)	35.50	0.00	-	8.48	3.78	2.24 (1.51, 3.33)
2003	54.30	21.50	2.53 (1.32, 4.84)	31.35	13.09	2.39 (0.87, 6.60)	8.72	0.00	-	8.27	4.46	1.85 (1.27, 2.70)
2004	27.92	3.96	7.06 (1.97, 25.29)	26.93	11.02	2.44 (0.82, 7.27)	0.00	7.14	0.00	6.64	3.32	2.00 (1.31, 3.05)
2005	36.83	15.04	2.45 (1.11, 5.39)	35.88	9.52	3.77 (1.26, 11.25)	35.49	11.10	3.20 (0.72, 14.29)	6.76	3.22	2.10 (1.36, 3.25)
2006	41.34	13.43	3.08 (1.40, 6.78)	47.00	9.35	5.03 (1.77, 14.27)	17.43	3.63	4.80 (0.44, 52.91)	9.24	3.41	2.71 (1.82, 4.02)
Overall IRR† and *P* for trend†										0.90	0.80	1.89 (1.60, 2.24)

*All incidences are per 100,000 women

† Adjusted for age, stage and year of diagnosis

Table 5 Urban–rural incidence rates* and incidence ratios of breast cancer by joint ER/PR status, by age-groups and overall in Gharbiah, 2001–2006[#]

Years	Urban–rural incidence and incidence ratios								
	Age-groups (Years)								
	0–29			30–39			40–49		
	Urban	Rural	Urban–rural IRR (95% CI)	Urban	Rural	Urban–rural IRR (95% CI)	Urban	Rural	Urban–rural IRR (95% CI)
ER+/PR+									
2001	0.00	0.12	0.00	15.22	3.51	4.33 (1.65, 11.40)	23.67	11.00	2.15 (1.04, 4.47)
2002	0.00	0.24	0.00	10.38	1.73	6.00 (1.62, 22.16)	27.68	5.83	4.75 (2.00, 11.29)
2003	0.86	0.12	7.21 (0.75, 69.29)	9.06	6.80	1.33 (0.55, 3.26)	37.22	11.46	3.25 (1.70, 6.22)
2004	0.00	0.23	0.00	7.79	5.00	1.56 (0.58, 4.18)	42.16	10.45	4.04 (2.11, 7.74)
2005	0.55	0.12	4.80 (0.44, 52.99)	12.04	0.55	22.00 (2.84, 170.41)	17.99	11.08	1.62 (0.76, 3.46)
2006	0.54	0.23	2.40 (0.34, 17.05)	11.83	6.99	1.69 (0.76, 3.78)	55.72	23.31	2.39 (1.49, 3.83)
ER−/PR−									
2001	0.59	0.12	4.80 (0.44, 52.99)	4.68	3.51	1.33 (0.38, 4.73)	14.79	15.23	0.97 (0.45, 2.10)
2002	0.29	0.36	0.80 (0.08, 7.70)	10.38	6.34	1.64 (0.68, 3.95)	14.57	5.00	2.91 (1.06, 8.02)
2003	0.57	0.12	4.80 (0.44, 52.99)	6.80	6.80	1.00 (0.38, 2.66)	14.31	13.10	1.09 (0.50, 2.41)
2004	0.28	0.35	0.80 (0.08, 7.70)	6.67	3.89	1.71 (0.58, 5.10)	19.67	13.66	1.44 (0.71, 2.92)
2005	0.28	0.12	2.40 (0.15, 38.41)	4.38	2.74	1.60 (0.43, 5.96)	9.69	7.91	1.22 (0.49, 3.22)
2006	0.00	0.00	–	3.23	2.15	1.50 (0.34, 6.70)	17.67	10.10	1.75 (0.81, 3.77)

Years	Urban–rural incidence and incidence ratios									Overall		
	Age-groups (years)											
	50–59			60–69			70+					
	Urban	Rural	Urban–rural IRR (95% CI)	Urban	Rural	Urban–rural IRR (95% CI)	Urban	Rural	Urban–rural IRR (95% CI)	Urban	Rural	Urban–rural IRR (95% CI)
ER+/ER+												
2001	64.14	18.05	3.55 (1.81, 6.98)	36.45	5.80	6.28 (1.70, 23,21)	45.06	7.51	6.00 (1.16, 30.91)	10.91	3.20	3.41 (2.29, 5.08)
2002	39.47	15.04	2.62 (1.21, 5.71)	23.93	17.13	1.40 (0.50, 3.92)	17.75	11.10	1.60 (0.27, 9.57)	8.16	2.88	2.84 (1.84, 4.36)
2003	62.06	14.78	4.20 (2.06, 8.57)	35.27	13.09	2.69 (1.00, 7.23)	17.44	3.64	4.80 (0.44, 52.91)	11.02	3.73	2.96 (2.04, 4.28)
2004	58.39	15.83	3.69 (1.84, 7.41)	34.63	5.51	6.28 (1.70, 23.22)	8.56	7.14	1.20 (0.11, 13.23)	10.56	3.24	3.26 (2.22, 4.80)
2005	57.48	14.29	4.02 (1.96, 8.25)	49.24	7.23	6.81 (2.22, 20.88)	42.14	24.59	1.71 (0.54, 5.40)	10.78	3.13	3.44 (2.31, 5.12)
2006	90.83	26.79	3.39 (1.98, 5.79)	48.37	19.54	2.48 (1.11, 5.53)	41.39	13.80	3.00 (0.81, 11.17)	17.07	6.59	2.59 (1.94, 3.46)
Overall IRR[†] and *P* for trend[†]										0.96	0.99	2.33 (1.68, 3.23)

Table 5 continued

Years	Urban–rural incidence and incidence ratios									Overall		
	Age-groups (years)											
	50–59			60–69			70+					
	Urban	Rural	Urban–rural IRR (95% CI)	Urban	Rural	Urban–rural IRR (95% CI)	Urban	Rural	Urban–rural IRR (95% CI)	Urban	Rural	Urban–rural IRR (95% CI)
ER−/PR−												
2001	16.03	8.33	1.92 (0.62, 5.97)	12.15	1.93	6.28 (0.65, 60.42)	0.00	3.76	0.00	4.07	2.78	1.47 (0.87, 2.46)
2002	28.95	13.68	2.12 (0.90, 4.98)	7.98	11.42	0.70 (0.14, 3.46)	26.62	0.00	–	5.76	2.96	1.95 (1.23, 3.09)
2003	28.44	17.47	1.63 (0.73, 3.63)	15.68	11.22	1.40 (0.39, 4.95)	8.72	0.00	–	5.20	3.89	1.34 (0.86, 2.08)
2004	20.31	2.64	7.70 (1.63, 36.25)	23.08	9.18	2.51 (0.77, 8.24)	0.00	7.14	0.00	5.43	2.84	1.91 (1.20, 3.03)
2005	17.49	14.29	1.22 (0.47, 3.16)	26.51	9.04	2.93 (0.93, 9.24)	33.72	10.54	3.20 (0.72, 14.29)	4.83	2.89	1.67 (1.03, 2.72)
2006	29.46	7.65	3.85 (1.44, 10.25)	37.21	5.33	6.98 (1.92, 25.37)	8.28	0.00	–	6.11	2.11	2.89 (1.76, 4.75)
Overall IRR† and *P* for trend†										0.81	0.76	1.72 (1.28, 2.32)

*All incidences are per 100,000 women

† Adjusted for age, stage and year of diagnosis

ER+/PR− and ER−/PR+ categories had too few cases and were excluded from this analysis

in other populations [15, 16]. Thus, other risk factors such as xenoestrogens might play an important role in increasing ER+ cancer in cities. Women in urban areas are prone to using more plastics and electrical appliances, household insecticides, detergents, cosmetics, etc. There have been multiple studies from various parts of the world that clearly demonstrate the higher presence and exposure to xenoestrogens in urban areas [26–30]. Our group showed in a previous study that urban women also have higher levels of 7,8-dihydro-8-oxo-2′-deoxyguanosine (8-oxo-dG) indicating higher DNA damage and thus higher exposure to carcinogens [38]. Since xenoestrogens have estrogenic effects and have been shown to be related to ER+ cancer [19–21], all the above exposures lead to higher incidence of breast cancer and ER+ cancer in urban areas. That apart, within rural areas incidence of breast cancer is almost similar for all HRS, a pattern more pronounced in the age-specific incidence. This demonstrates that exposure to estrogenic and non-estrogenic risk factors are quite similar in rural areas while in urban areas exposure to estrogenic factors is higher.

ER status of breast cancer is also related to the period in women's life when they are exposed to various risk factors and these insights follow from studies into breast development and stem cell research. There are three critical periods in the development of mammary glands: the intrauterine period especially just before birth, the peripubertal period, and the period of pregnancy and lactation [39]. Research into mammary stem cells, which are now considered to be the origin of breast cancer [40–43], shows that during the intrauterine period all stem cells which are the progenitor stem cells, are ER− [44, 45]. Postnatally these ER− stem cells differentiate into ER+ cells which later form mammary glands during puberty under the influence of estrogen [44]. It is quite possible that early life exposures during the intrauterine period or around birth affect the progenitor stem cells which at that time are predominantly ER− which would then lead to ER− cancer in younger ages. Exposure to xenoestrogens in early life is quite plausible in the light of studies showing excretion of xenoestrogens in human milk in Egypt [46] and across the world [47, 48]. However, progenitor stem cells are few in number and quite hardy and resistant to mutations [49] and as such in populations exposed to estrogenic risk factors early in life—endogenous or exogenous—ER− cancer will be higher than in unexposed populations but still lower than ER+ cancer within the same exposed population. ER+ cancer must be higher in exposed populations because ER+ stem cells are more numerous later in life and are less resistant to mutations [49]. This explains the higher incidence of breast cancer later in life after menopause in exposed or urban populations when the ER+ stem cells accumulate maximum number of mutations according to the multi-hit theory of carcinogenesis (which indicates

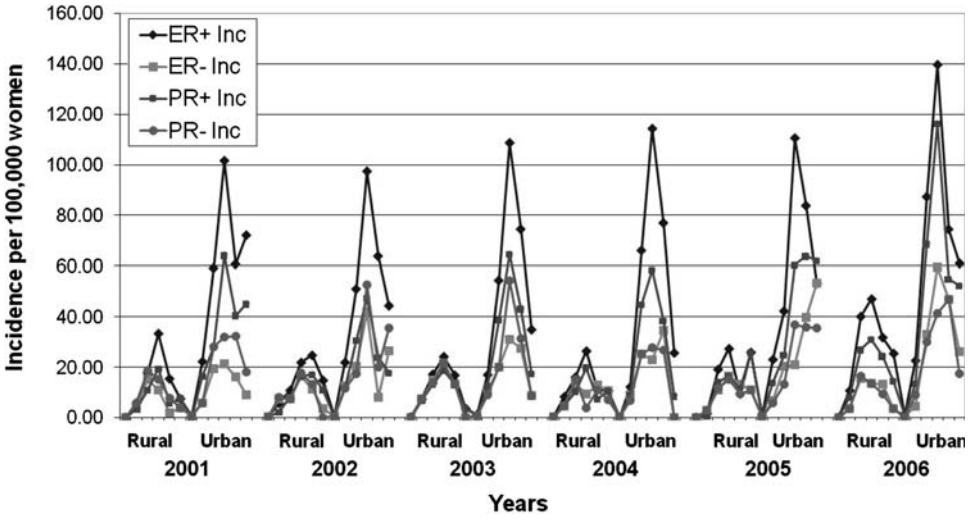

Fig. 1 Age-specific urban–rural incidence of breast cancer by hormone receptor status in Gharbiah, 2001–2006. All incidences are per 100,000 women. There are 6 age-groups: 0–29, 30–39, 40–49, 50–59, 60–69, and 70 or more, each represented by a point on the *graph* for each year in that sequence

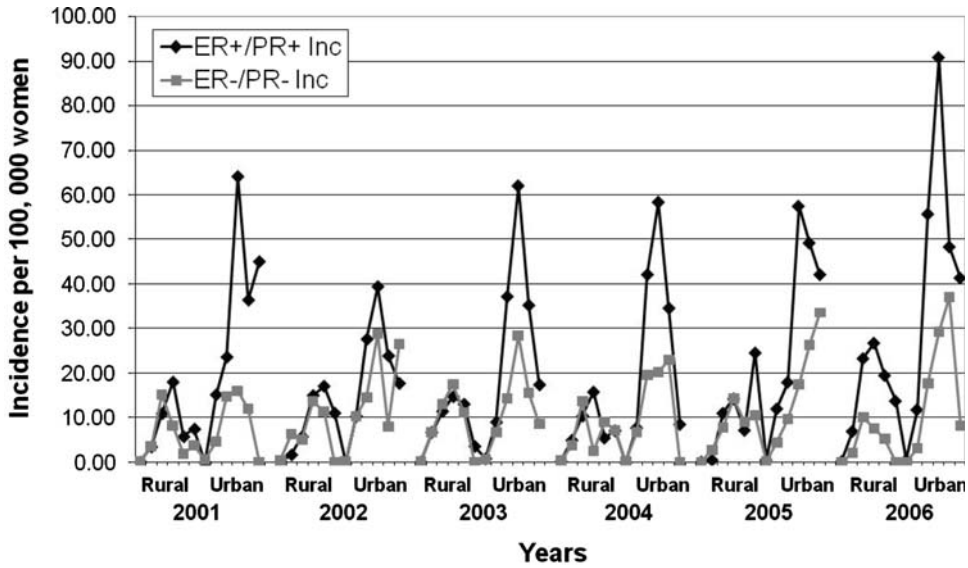

Fig. 2 Age-specific urban–rural incidence of breast cancer by joint hormone receptor status in Gharbiah, 2001–2006. All incidences are per 100,000 women. There are 6 age-groups: 0–29, 30–39, 40–49, 50–59, 60–69, and 70 or more, each represented by a point on the *graph* for each year in that sequence. ER+/PR− and ER−/PR+ categories had very few cases and were excluded from this *graph*

that a normal cell must be subjected to multiple "hits" or exposures which result in multiple mutations over time in genes regulating cell growth, eventually resulting in uncontrolled cell growth and tumor formation). This also explains the fact that urban women are more exposed to xenoestrogens throughout life and thus have higher incidence of both ER+ and ER− cancer.

PR expression is under the control of ER expression [50] and thus the pattern of PR expression closely follows ER expression. However, not all ER+ tumors express PR and thus PR+ incidence is lower than ER+ incidence. Also, since some ER+ tumors are PR−, PR− incidence must be slightly higher or similar to ER− incidence, a pattern seen clearly in Gharbiah. Breast cancer incidence by joint HRS can also be explained due to above reason since ER+/PR+ incidence is the highest followed by ER−/PR− incidence. ER+/PR− incidence is next since some ER+ tumors don't express PR. ER−/PR+ incidence is the lowest since in the absence of ER expression PR expression is very unlikely. Age-specific incidence by joint HRS was limited to ER+/PR+ and ER−/PR− cancer since the number of cases in other two joint hormone receptor categories was too low for some age-groups. ER+/PR+ cancer has the highest incidence for most age-groups within urban areas and also when compared with rural areas. Within rural areas incidence of ER+/PR+ and ER−/PR− cancer is similar for most age-groups in all years which again clearly shows that estrogenic and non-estrogenic exposures are almost similar in rural areas.

One of the main limitations of this study is the absence of HRS information for all the cases for the 6-year period. It can be seen that the incidence of cases with unknown HRS has remained almost similar across the years with decrease in 2006 since we had information on more

number of cases for this year. Still this did not affect the urban–rural differences of breast cancer by HRS in 2006 substantially. We also compared cases with known HRS and unknown HRS and cases from entire Gharbiah based on important baseline factors like urban–rural distribution, age and AJCC stage and found the three categories of cases to be similar to each other in these distributions. Also, a number of cases with missing HRS information were diagnosed by FNAC and many of these cases were having metastatic disease (Stage 4) which is more likely to be rural and ER−. Detection of HRS of such cases would increase ER− incidence in rural areas which will not affect ER+ incidence in urban areas. Thus, it is unlikely that absence of HRS information affected our findings in this study.

Another confounder could be the difference of HRS determination among pathology laboratories in Gharbiah. However, HRS determination started routinely in 2001 when HRS determination methods had become quite standard across the world. Also, in Gharbiah there are only a handful of pathology laboratories that conduct HRS determination and they import their antibodies from a single vendor. We obtained details of the procedure from various laboratories and determined that HRS determination was similar for all sites since 2001. In addition, patients get the tumor slides examined by multiple laboratories for second opinion and the registry routinely compares data across pathology laboratories for consistency. Thus, it is unlikely that differences in HRS determination methods will affect our findings [14]. In addition, if any differences exist, they are more related to classifying the degree of positivity and not regarding classifying tumors as positive and negative. Since we have based our analysis in this paper on classifying tumors into positive or negative, the effects of any subjective difference between laboratories are quite minimal.

Overall we showed that urban women have a higher incidence of ER+ incidence than rural women and xenoestrogens might be a significant cause of this in developed countries and urban areas of developing countries. The pattern of distribution of HRS in urban and rural areas also points towards probable timing of exposure to xenoestrogens. Although we did not have information on xenoestrogen exposure at the individual level, we have already planned a study in near future looking at urban–rural differences in urine levels of xenoestrogens in peripubertal females. We also need future studies investigating correlations of xenoestrogen exposure with HRS, examining the molecular mechanisms by which xenoestrogens lead to ER+ cancer, and the role of mammary stem cells which might hold important clues regarding critical periods of exposure and better ways of prevention and treatment of breast cancer.

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