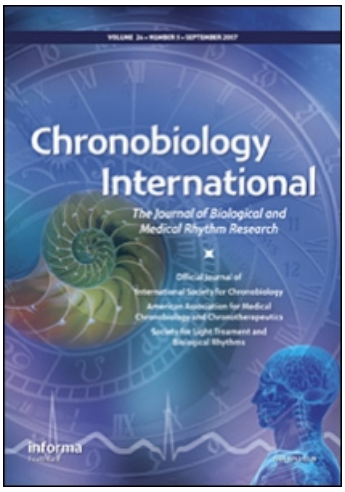

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Light at Night Co-distributes with Incident Breast but not Lung Cancer in the Female Population of Israel

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LIGHT AT NIGHT CO-DISTRIBUTES WITH INCIDENT BREAST BUT NOT LUNG CANCER IN THE FEMALE POPULATION OF ISRAEL

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Recent studies of shift-working women have reported that excessive exposure to light at night (LAN) may be a risk factor for breast cancer. However, no studies have yet attempted to examine the co-distribution of LAN and breast cancer incidence on a population level with the goal to assess the coherence of these earlier findings with population trends. Coherence is one of Hill's "criteria" (actually, viewpoints) for an inference of causality. Nighttime satellite images were used to estimate LAN levels in 147 communities in Israel. Multiple regression analysis was performed to investigate the association between LAN and breast cancer incidence rates and, as a test of the specificity of our method, lung cancer incidence rates in women across localities under the prediction of a link with breast cancer but not lung cancer. After adjusting for several variables available on a population level, such as ethnic makeup, birth rate, population density, and local income level, a strong positive association between LAN intensity and breast cancer rate was revealed ($p < 0.05$), and this association strengthened ($p < 0.01$) when only statistically significant factors were filtered out by stepwise regression analysis. Concurrently, no association was found between LAN intensity and lung cancer rate. These results provide coherence of the previously reported case-control and cohort studies with the co-distribution of LAN and breast cancer on a population basis. The analysis yielded an estimated 73% higher breast cancer incidence in the highest LAN exposed

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communities compared to the lowest LAN exposed communities. (Author correspondence: portnov@nrem.haifa.ac.il)

Keywords Breast cancer, Light at night, Melatonin Lung cancer

INTRODUCTION

A recent theory (Davis et al., 2001; Pauley, 2004; Stevens, 1987, 2005) states that excessive exposure to light at night (LAN) increases breast cancer risk. A variety of mechanisms have been proposed, including suppression of melatonin secretion by the pineal gland leading to increased tumor growth (Blask et al., 2005), effects on immune and thermoregulatory functions (Haim et al., 2005; Nelson, 2004), and/or direct disruption of clock gene function in the suprachiasmatic nuclei (SCN; biological clock) leading to alterations in cell cycle regulation in breast tissue (Stevens & Rea, 2001; Stevens et al., 2007). In contrast to breast cancer, lung cancer has a known dominant cause, smoking, which accounts for about 90% of cases (American Cancer Society [ACS], 2006). Currently, there is no evidence suggesting that LAN exerts an effect on lung cancer development.

The concentration of melatonin in blood is normally high at night and low during the day (Wehr, 2001), and its production by the pineal gland is driven by the SCN, which is in turn influenced by the intensity, duration, and spectral power distribution of the radiation on the non-image forming photoreceptors of the retina (Brainard et al., 2001). Among the variety of its biological actions, melatonin has oncostatic effects (Blask et al., 1992, 2003) and may thus have an effect on the proliferation of cancer cells. In particular, Blask et al. (2005) demonstrated LAN caused growth enhancement of human breast tumor tissue in the nude rat model.

Based on cohort and case-control studies in specific subpopulations, the evidence in support of LAN increasing the risk of breast cancer is limited but generally supportive. Several predictions of the LAN theory have been examined, including that shift-working women would be at higher risk (Davis et al., 2001; Hansen, 2001; Lie et al., 2006; Schernhammer et al., 2001); blind women (Hahn, 1991; Kliukiene et al., 2001; Verkasalo et al., 1999) and long sleepers (Pinheiro et al., 2006; Verkasalo et al., 2005) would be at lower risk; and light level in the bedroom at night would be related to risk (Davis et al., 2001; O'Leary et al., 2006). To date, the strongest and most consistent evidence is that women with an occupational history of non-day shift work are at higher risk; this has resulted in a classification of "shift work" as a 2A probable human carcinogen by the International Agency for Research on Cancer (IARC; see Straif et al., 2007).

The present study attempts to investigate the link between local LAN level and incidence of breast and lung cancer in women using cancer

rates and LAN intensity data available for 147 individual urban localities in Israel. In particular, the present analysis attempts to answer the question, Are the epidemiological studies among female shift workers and blind women coherent with respect to the co-distribution of breast cancer incidence of women and LAN levels in communities (i.e., at the population level)? Such coherence is an important consideration in the assessment of causality as proposed by Hill (1965). Hill describes this attribute as the seventh of his nine viewpoints on what to consider when attempting to infer the causality of an association between environmental exposures and incidence of disease in populations. We predicted an absence of a correlation between LAN and lung cancer, because, as previously mentioned, there is no evidence suggesting that LAN exerts any effect on the development of lung cancer. Thus, finding a correlation between LAN and breast cancer, on the one hand, and no correlation between LAN and lung cancer, on the other, in women would constitute supportive evidence for the specificity of our analysis.

MATERIALS AND METHODS

Israel as a Case Study

Israel is a small and densely populated country with a total land area of about 22,000 km^2. The majority of the country's population is concentrated around the three major cities of Jerusalem, Tel-Aviv, and Haifa, where nearly 40% of the country's population (7,100,000, as of 2006) reside. Economically, the country is well developed with the Gross Domestic Product (GDP) being USD 26,800 per capita, which is similar to that of Greece, New Zealand, and South Korea (CIA, 2006).

As in other developed countries, Israel has high levels of LAN, caused by extremely high population densities (ca. 300 residents per km^2 overall) and the above-mentioned geographic concentration of economic activities in a few developed foci. This unevenness of geographic development and resulting variability of LAN levels (see Figure 1) are considered an advantage of the present study, because they provide us with localities characterized by distinctively different LAN levels, thus increasing the intra-sample variability of LAN exposure levels. (A color version of Figure 1 is available in the online version of this article.)

Three other considerations are also relevant for the present analysis. Israel's population is ethnically heterogeneous. It is composed of one major ethnic group (Jews, both living locally for generations and immigrates from around the world after the establishment of the State of Israel in 1948), plus a number of minority groups (Arabs, Druze, and Circassians). With the exception of a few population centers (Jerusalem, Haifa, Acre, and Ramle—cities with a mixed Jewish and Arab population), the urban localities

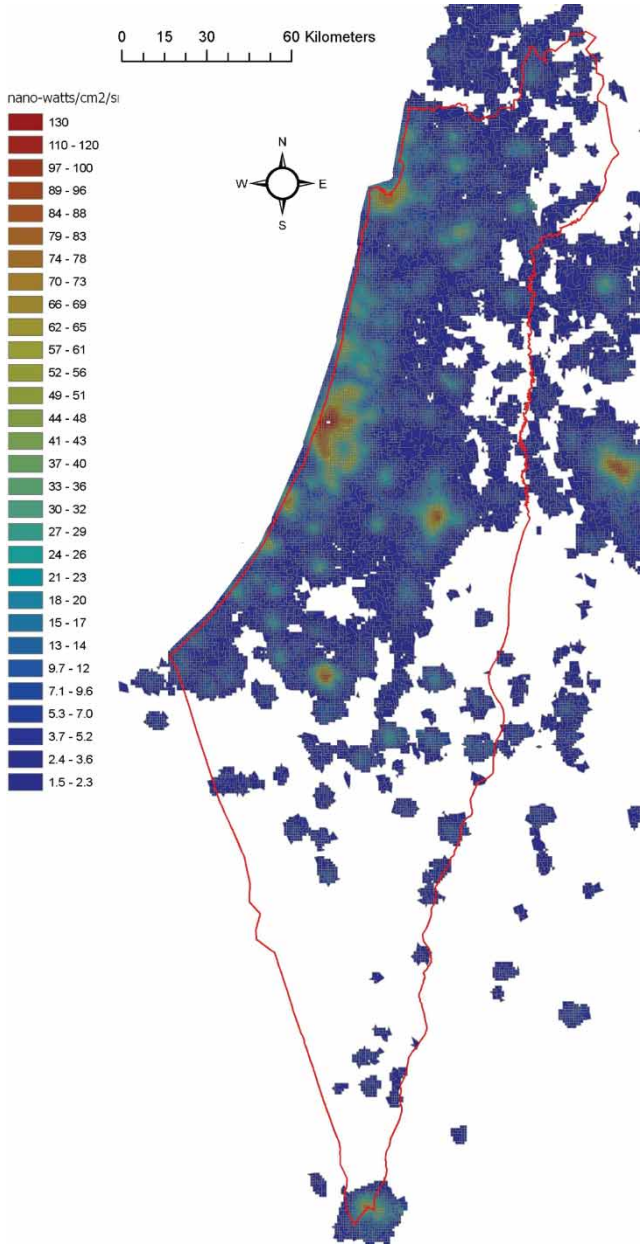

FIGURE 1 LAN intensity levels (nanowatts/cm^2/sr) according to nighttime satellite image data (source: DMSP 2004).

in Israel are ethnically unmixed (i.e., either Jewish- or Arab-populated). Overall, the Jewish population (i.e., 80% of the total population) has higher income levels and higher rates of labor force participation (about 52%, as opposed to about 37% among the Arabs). Labor force participation is

especially low among minority women, which is explained by cultural and family traditions. The Jewish population of Israel is ethnically heterogeneous as well. The mass wave of immigration to Israel since 1948 has included large numbers of immigrants from North Africa and Asia. Many of these immigrants found it difficult to adjust to life in the Western-oriented society established by the founders of modern Israel and, consequently, found themselves delegated to the lower socio-economic strata of Israeli society. Regions populated predominately by this category of former immigrants tend to have relatively low income rates (Portnov & Erell, 2003). Breast cancer incidence rates are higher in Jewish and more affluent communities (Israeli Ministry of Health [IMOH], 2004), and there are substantial differences in birth rates elsewhere, 37.2 new births per 1000 residents in minority cities vs. 18.2 new births per 1000 residents (Israel Central Bureau of Statistics [ICBS], 2004).

Selection of Localities and Dependent Variables

This study and its conduct conformed to the ethical standards of this journal (Touitou et al., 2006). Statistical data on age-standardized rates per 100,000 population (ASR) of female breast and lung cancer for the present analysis were obtained from the Israel National Cancer Registry (IMOH, 2004). In this registry, such rates are available only for localities of more than 5,000 residents. Therefore, only 147 localities (i.e., all the localities above this population threshold) were covered by the present study. For these localities, the cancer rates in 1998–2001 were calculated per 100,000 residents (age-standardized to the "world standard population," as commonly done in similar studies (Bray et al., 2004; Luke et al., 2006; Roychoudhuri et al., 2006). In Israel, the population-based national cancer registry covers the entire country, and completeness of the registry is greater than 95%. There are more than 30 major medical facilities, both governmental and public, that report to the registry. Cancer reporting has been mandatory since 1982, and routine quality assurance measurements are undertaken to ensure completeness and accuracy of the registration cases (IMOH, 2004).

LAN Data

In order to represent the LAN levels in the localities, a radiance-calibrated satellite image of nighttime illumination in Israel was obtained from the U.S. Defense Meteorological Satellite Program (DMSP, 2004). The satellite image in question reports average night-light intensity in 1996/97, measured in light radiance units (i.e., nanowatts/cm^2/sr). The image represents a fraction of the light escaping into space and detected by the satellite's sensors. Although these satellite measurements are a

magnitude lower than actual LAN levels detected on the ground, they accurately represent the relative levels of night-light intensity observed in the localities (see Figure 1).

GIS Analysis

In recent years, Geographic Information Systems (GIS) have become an important research tool for cancer-related studies (Banerjee et al., 2003; Krieger et al., 2002; Maheswaran et al., 2002; O'Leary et al., 2004; Scott et al., 2002). In these studies, GIS are used, for example, to calculate the distance between residences and hazardous waste sites, account for the spatial clustering and variation of cancer cases, and capture spatio-temporal heterogeneity in survival patterns. In the present study, GIS technology was used for matching the layers of cancer rates with local LAN levels obtained from satellite images, on the one hand, and relevant socio-economic data (income levels, population size of localities, etc.), on the other. GIS tasks were performed using the "spatial join" tool in the ArcGIS 9 ™ software (Minami et al., 2000). The spatial join operation involves matching rows from different geographic layers (i.e., maps) to the target layer based on the spatial relationship between them. In the present study, LAN levels from the satellite image were added to the target layer containing cancer rates and relevant socio-economic data (income levels, population size of localities, etc.).

Statistical Analysis

Statistical analysis of data was performed in two phases. In the first phase, analysis of variance (ANOVA) was applied to determine whether localities characterized by different ground LAN intensities exhibited significantly different cancer rates. To this end, the entire set of localities under study (147) were split into three groups—low, medium, and high LAN exposure localities—using the Jenks natural break method. The Jenks classification determines the best arrangement of values into classes by comparing the sum of squared differences of values from the means of their classes. It thus identifies "break points" in the data values and picks the class breaks that best group similar values and maximizes differences between classes (Jenks, 1967; Minami et al., 2000). In the second phase, ordinary least squares (OLS) regression analysis was used to assess the association between age-standardized cancer rates and local LAN intensities obtained from satellite image data. Because in our dataset, the dependent variables (i.e., female breast and lung ASRs per 100,000 residents of a locality) were on the ratio scale, OLS regression was the preferred analysis tool rather than the Poisson and logistic regressions approaches commonly used in environmental studies and

are more suitable for count and categorical data (Long, 1997). The analysis was performed separately for all cancer rates using the following linear model:

$$\begin{aligned}\text{Cancer incidence rate} = {} & \text{constant} + \text{B1} \times (\text{majority/minority}) + \\ & \text{B2} \times (\text{per capita income}) + \text{B3} \times (\text{LAN}) + \text{B4} \times (\text{population size}) + \\ & \text{B5} \times (\text{birth rate}) + \text{B6} \times (\text{population density}) + (\text{random error term})\end{aligned}$$

where B1, . . ., B6 are regression coefficients. During the analysis, several other functional forms of the model (e.g., log-linear and double-log forms) were tested, and only the results of the best performing (linear) model are reported. To account for some potential confounders, the following data were obtained from the Israel Central Bureau of Statistic's annual report on Local Authorities in Israel—Physical Data (ICBS 2004).

Majority/Minority Composition

In Israel, there is a clear segregation between localities that allows one to identify the makeup of the population. This is important because cancer rates in the Jewish sector are much higher than among the minority population (IMOH, 2004).

Per Capita Income

Per capita income is a commonly used measure of population welfare that reflects differences in the diet and lifestyle of different socio-economic strata. Several previous studies indicated that cancer rates tend to be higher among high than low-income strata (ACS, 2006; Bray et al., 2004). In addition, the inclusion in the analysis of the per capita income variable helps to differentiate between the different ethnic makeup within the Jewish population.

Population Size

Thousands of residents typically encompass the demography and economy of communities. Large, as opposed to small, cities are often characterized by more ethnically heterogeneous populations where there is greater physiological stress due to high residential densities and traffic congestion. Population size of localities may also serve as a proxy for the intensity of LAN that may not be detected by satellite sensors, such as illumination inside public buildings, public transportation, etc. The larger the population of a locality, the greater the illumination in transportation and public facilities. In theory, the intensity of LAN on a satellite map could serve as a proxy measure for population density (MANTLE Project,

2007). Therefore, the density variable (the number of residents per km^2 of built area of a locality) was added to the regression models to examine such a possibility.

Birth Rate

Although birth rates (per 1,000) of communities do not capture the full impact of reproductive factors associated with breast cancer, high birth rates are known to be negatively associated with breast cancer; multiple pregnancies reduce breast cancer risk, while nulliparity tends to increase it (ACS, 2006). The inclusion of the birth rate variable in the analysis thus attempts to take the aspect of parity into account.

During the analysis, multicollinearity, normality, and homogeneity of variance assumptions were tested, and the results were found satisfactory. The regression residuals were also tested for the presence of spatial autocorrelation, using Moran's I global autocollinearity test (Anselin, 1999), and no significant spatial clustering of residuals was found.

Analysis of Local Spatial Autocorrelation

In the present study, the analysis of Local Spatial Autocorrelation (LSA) was used to detect the geographic clustering of female breast cancer rates (female lung cancer was not analyzed, as it is only used in the regression analysis as a control). The Getis-Ord ($G_i^*(d)$) statistic, used to this end, is reported as standard normal z-values and evaluates each point within a network of sites, thus helping to determine the relationship between the values observed around the target point and the global mean (Getis & Ord, 1992). This statistic is easy to interpret: a significant and positive $G_i^*(d)$ indicates that location i is surrounded by relatively large values with respect to the global mean (i.e., "peak-value clusters"), whereas a significant and negative $G_i^*(d)$ indicates that location i is surrounded by relatively small values (i.e., "dip-value clusters").

RESULTS

"Hotspot" Analysis

The results of the LSA analysis are shown in Figure 2. (A color version of Figure 2 is available in the onlive version of this article.) The large red dots indicate clusters of adjacent localities with very high breast cancer rates, while large green dots symbolize clusters of adjacent localities with significantly low (with respect to the global mean) values of breast cancer rates ($p < 0.05$). A clear clustering of significantly low breast cancer rates ($p < 0.05$) are apparent in the northern part of the country (see clusters of

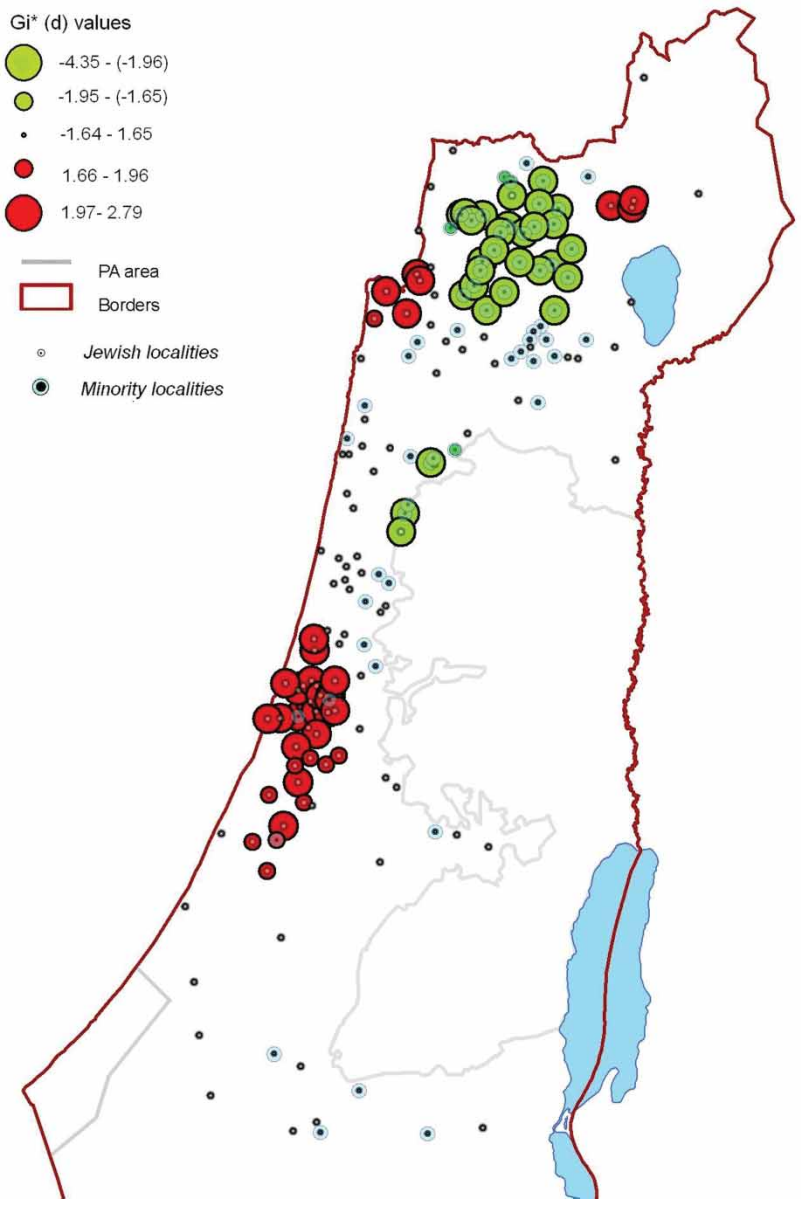

FIGURE 2 "Hotspot" analysis of breast cancer rates. *Note:* Red circles mark clusters of adjacent localities with significantly high rates of cancers (relative to the global mean), while green circles mark geographic clusters of localities with significantly low cancer rates.

green dots in the upper right corner of the map). As the analysis indicates, most of them are localities with a predominantly minority population that are characterized by relatively low infrastructure development and correspondingly relatively low LAN level. On average, the LAN of localities with

minority populations is 11.70 nanowatts/cm^2/sr, as opposed to Jewish localities in which the average LAN is 26.34 nanowatts/cm^2/sr. Clusters of localities exhibiting significantly high rates of breast cancer are evident. Most of these are located in the metropolitan areas of Tel Aviv and Haifa (see the clusters of large red dots in the center and the upper corner of the map), which have high urban infrastructure and socio-economic development and may thus afford extensive illumination systems (which themselves leak light to the outdoor surroundings) both around public places and transportation nodes. This is consistent with the average LAN values (see Figure 2).

General Trends

Table 1 reports the average rates of breast and lung cancers across three groups of localities characterized by different LAN levels as determined by Jenks's natural break method (i.e, <30 nanowatts/cm^2/sr, low; 30–55 nanowatts/cm^2/sr, medium; and >55 nanowatts/cm^2/sr, high). The average cancer rates tend to increase in line with ground LAN intensity (70.31, 95.92, and 96.94 cases per 100,000 residents for female breast cancer and 8.62, 11.25, and 15.05 for female lung cancer in the low, medium, and high LAN groups, respectively). However, only for the breast cancer rates are these differences statistically significant (Welch = 32.158, Brown-Forsythe = 39.733, $p < 0.001$; see Table 1).

Multivariate Analysis

Although the initial investigation demonstrated a significant increase in breast cancer ASR in line with rising ground LAN levels (see Table 1),

TABLE 1 Age-Standardized Rates of Female Breast and Lung Cancer per 100,000 Residents of Localities with Different Light at Night (LAN) Intensities

LAN intensity group of localities*	Breast cancer	Lung cancer
Low	70.31	8.62
Medium	95.92	11.25
High	96.94	15.05
Equality of group means tests		
Welch	32.158 (<0.001)	3.812 (0.04)
Brown-Forsythe	39.733 (<0.001)	3.403 (0.07)

Method: ANOVA, Equality of group means test. Significance levels are in parentheses.

Group membership is determined by Jenks' natural break method: <30 nanowatts/cm^2/sr (low); 30–55 nanowatts/cm^2/sr (medium), and >55 nanowatts/cm^2/sr (high).

TABLE 2 Factors Affecting Female Breast and Lung Cancer Rates in Localities

	Dependent variable	
Explanatory variable	Breast (Ln)*	Lung (Ln)*
Constant	3.582 (14.244)§	2.059 (5.810)§
Majority/minority	−0.548 (−5.874)§	−0.198 (−1.415)
Per capita income	0.076 (2.314)§	0.045 (1.029)
LAN (Ln)	0.121 (1.932)‡	−0.013 (−0.152)
Population size	−2.41E-05 (−0.040)	3.77E-007 (0.518)
Birth rates	0.002 (0.704)	0.006 (1.435)
Density	0.008 (0.966)	−0.001 (−0.093)
Number of observations†	147	147
R^2	0.505	0.050
R^2 adjusted	0.427	−0.003
F	19.072§	0.939

Method: ordinary least squares (OLS) regression; dependent variable: cancer rates (Ln) per 100,000 residents.

*Regression coefficient (*t*-values are in parenthesis).

†Number of valid observations, list-wise.

‡Significant at a $p < 0.05$ level, §significant at a $p < 0.01$ level.

Abbreviations: breast = breast cancer, lung = lung cancer (female).

ANOVA provides only the indication of the presence of such a relationship, because it does not adjust for confounding or modifying factors (e.g., differences in welfare level, population density, or local birth rate). To examine the possibility that the result might change if the aforementioned potential confounders are taken into account, multiple regression analysis was conducted. Table 2 reports the regression models in which ground LAN levels are controlled by the ethnic makeup, population size of localities, population density, local incomes, and local birth rate in assessing the association with female breast cancer as well as lung cancer. The "breast cancer model" appears to provide a reasonably good fit ($R^2 = 0.505$) in contrast to the lung cancer model, in which the fit is very low ($R^2 = 0.050$). Importantly, the breast cancer model also has a high degree of generality ($F = 19.072$, $p < 0.001$). As Table 2 shows, only the breast cancer rates are positively associated with LAN ($B = 0.121$, $t = 1.932$, $p < 0.05$), while the lung cancer rates are not ($B = -0.013$, $t = -0.152$, ns).

Per capita income is also positively associated with age-standardized breast cancer rates ($t = 2.314$, $p < 0.001$), indicating that wealthy localities exhibit, *ceteris paribus*, higher rates of breast cancer.

Majority/minority population composition was negatively associated only with female breast cancer ($t = -5.784$, $p < 0.001$), indicating that the minority group (non-Jewish population) tends to exhibit lower rates of breast cancer, a finding that is in agreement with previous studies of cancer in Israel (IMOH, 2004).

TABLE 3 Factors Affecting Breast Cancer Rates in Localities

Variable	B*	t†
Significant variables (variables in the model)		
Constant	3.748	19.181§
Majority/minority	−0.547	-6.083§
LAN (Ln)	0.141	2.788§
Per capita income	0.057	1.980‡
Number of observations#	147	
R^2	0.444	
R^2 adjusted	0.432	
F	38.033§	
Insignificant variables (excluded variables)		
Population size		0.342ns
Birth rates		0.707ns
Density		1.015ns

Method: stepwise regression; dependent variable: female breast cancer rates (ln) per 100,000 residents.

*Regression coefficient.

†*t* Values.

‡Significant at a $p < 0.05$ level, §significant at a $p < 0.01$ level.

#Number of valid observations, list-wise.

NS = not significant.

Although the multicollinearity of variables in the analysis was tested and found within tolerable limits (tolerance < 1.8), even this relatively low level of multicollinearity may bias regression estimates. Therefore, we used the stepwise multiple regression (SMR) method to include only statistically significant variables in the resulting model. The results are reported in Table 3. As the model shows, three variables (i.e., majority/minority compostion, LAN, and per capita income) emerged as statistically significant ($p < 0.05$). As in the previous OLS model (see Table 2), breast cancer rates are positively associated with LAN ($B = 0.141$, $t = 2.788$, $p < 0.01$), higher in wealthy localities ($B = 0.057$, $t = 1.980$, $p < 0.05$) and lower in minority ($B = -0.547$, $t = -6.083$, $p < 0.01$) population localities. Notably, other

TABLE 4 Change in Female Breast Cancer Age-Standardized Rates as a Function of Rising Ground LAN Intensity (Model Sensitivity Test)

	LAN	Breast cancer rate	% Change
Minimum	2.26	60.88	—
Average	20.63	83.26	36.75
Maximum	112.01	105.56	26.79

Note. Based on the model reported in Table 3.LAN values are in nanowatts/cm^2/sr; breast cancer values are per 100,000 residents. The values of the fixed variables are set as follows: average per capita income NIS$4363 (average value for all localities under study) and majority/minority=0 (Jewish towns).

controls, such as population size, birth rates, and population density, are filtered out as statistically insignificant ($p > 0.05$; see Table 3).

As Table 4 shows, with the values of all other controlled variables (see Table 3) fixed, the observed increase in LAN level from 2.26 nanowatts/cm^2/sr (minimum LAN exposure) to 20.63 nanowatts/cm^2/sr (average LAN exposure) in the sample of localities corresponds to an increase of 37% in female breast cancer ASR.

DISCUSSION

The hypothesis that LAN increases risk of breast cancer causation is consistent with the prediction that blind women would be at reduced risk and shift-working women would be at high risk; studies so far support these predictions (Davis et al., 2001; Feychting et al., 1998; Hahn, 1991; Hansen, 2001; Kliukiene et al., 2001; Lie et al., 2006; Schernhammer et al., 2001, 2006; Verkasalo et al., 1999). Although the studies conducted thus far appear to suggest that excessive exposure to LAN by women is associated with elevated risk of developing breast cancer, this conclusion must be coherent with the observed co-distribution of LAN and breast cancer on the population level. The aim of the present research was to test two predictions at the general population level: that there would be a link between LAN exposure and the incidence of female breast cancer, and that there would not be a link to female lung cancer. Lung cancer was chosen as a "negative control" to assess the specificity of the analytic approach. The results supported both predictions.

As described in the methods and results sections, local income level was adjusted for because income is associated with risk of breast cancer (ACS, 2006; Bray et al., 2004; Snell, 1995). It is not clear what aspect of income or affluence is causal of this association. In regard to the LAN theory, income may serve in part as a proxy for artificial light intensity inside households. For instance, high socio-economic groups may be less concerned than lower socio-economic groups with high electricity costs and thus use more illumination in their houses (Gram-Hanssen & Petersen, 2004). The satellite data provided us with ambient, LAN levels external to inside the home. Both LAN levels and local income were positively associated with risk of breast cancer. Similarly, population size of localities may serve in part as a proxy for the intensity of LAN that may not be detected by satellite sensors, such as illumination inside public buildings, in public transportation, etc. The larger the population of a locality, the greater the illumination in transportation and public facilities. Due to the limitation of the data availability, occupation, reproductive delay, alcohol consumption, smoking, and other potentially important risk factors were not included in the analysis, although the per capita income variable may have captured some of their effects.

In general, environmental health problems can be approached at four different levels: the micro-level, individual level, population level, and

ecosystem level (Pearce, 1996). Each level has its own strengths and weaknesses. While micro- and individual-level studies tend to be more accurate and sensitive, population and ecological level studies are pivotal in defining the key public health problems that ought to be addressed (Pekkanen & Pearce, 2001). In many cases, environmental health problems are better addressed by large-scale, population-based investigations than individual-level investigations due to the occurrence of a large number of low-level exposures (Pekkanen & Pearce, 2001). However, a substantial drawback of population-based studies is those associations that occur at an aggregated level may be subject to ecological confounding or fallacy (Portnov et al., 2007; Robinson, 1958; Selvin, 1958). Several techniques were used to reduce the possibility of ecological confounding: separate analyses were performed for sub-populations (grouping by ethnic origin) and adjusted for some potential confounders (Elliot et al., 1996; Morgenstern & Thomas, 1993), including income level, ethnic makeup of localities, and birth rate.

Because the results of the present study are location-specific, future studies should include a comparison of these results to those obtained in other countries with similar geographic and socio-demographic characteristics, thus validating the generality of the present findings. Furthermore, in order to assess the importance of photoperiod regimes on human seasonal adaptations, it may be desirable to compare the present results with those of follow-up studies conducted in countries characterized by extreme differences in seasonal photoperiod regimes. Using finer spatial grid for ground LAN intensities (e.g., higher resolution satellite images and in situ measurements) is another needed addition to our research. With such high-resolution data, it is possible to do a more precise analysis of association between LAN levels and hormone-dependent cancer rates (down to individual LAN exposure levels). The addition of more potential confounders (e.g., smoking, alcohol consumption) to the multivariate analysis should also be considered.

The link between LAN exposure and female breast cancer rates found in this study, as well as absence of link to female lung cancer, further strengthens previous studies concerning the relation between LAN and breast cancer in women by providing evidence of coherence as described by Hill (1965). This conclusion must be viewed in light of the known impacts of illumination on melatonin production and secretion by the pineal gland, its relation to a variety of hormones that are involved in the development of breast cancer (Pauley, 2004; Reiter, 1991; Stevens, 2005), and the limitations of population-based studies outlined in the previous sections.

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