# Breast Cancer in Arab and Jewish Women in Northern Israel: A Retrospective Database Study

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**ABSTRACT** **Background:** In Israel, breast cancer prevalence is lower among Arab than Jewish women, but incidence is increasing among Arab women at a younger age.

**Objectives:** To explore differences between Arab and Jewish women with breast cancer with respect to age at diagnosis, associated risk factors, and use of hormonal medications.

**Methods:** We conducted a retrospective database study comparing Arab and Jewish women with breast cancer focusing on age at diagnosis, smoking history, obesity, and previous hormonal medication usage, including oral combined contraceptive pills (OCCP), progestogens, hormonal medications for treatment of infertility, and hormone replacement therapy (HRT).

**Results:** The study included 2494 women who were diagnosed with breast cancer during 2004–2015. Age at diagnosis was lower among Arab women (50.7 ± 13.1 years vs. 55.4 ± 12.6 years, $P < 0.0001$). The rate of smoking was higher among Jewish women (16.0% vs. 4.3%, $P < 0.0001$). The rate of obesity was higher in Arab women older than 50 years at diagnosis (59.0% vs. 42.4%, $P < 0.0001$). Arab women demonstrated a lower overall chance of previous use of all types of hormonal medications (odds ratio [OR] 0.6, 95% confidence interval [95%CI] 0.6–0.8) compared to Jewish women. Arab women were more likely to have used progestogens (OR 1.7, 95%CI 1.4–2.2) and medications for treatment of infertility (OR 2.3, 95%CI 1.5–3.4) and less likely OCCP (OR 0.4, 95%CI 0.3–0.6) and HRT (OR 0.4, 95%CI 0.3–0.5).

**Conclusions:** Previous use of hormonal medications may contribute to incidence of breast cancer in Arab women.

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**KEY WORDS:** Arabs, breast cancer, hormones, Jews, risk factors

Breast cancer is the most prevalent malignancy in women [1]. Epidemiology of breast cancer shows differences between populations around the world, with higher incidence rates in North America, Australia/New Zealand, and Western and Northern Europe, and lower incidence rates in Asia and sub-Saharan Africa [1,2].

In the ABREAST research study, Hortobagyi and colleagues [3] reviewed the global breast cancer burden in 2005, reporting the highest incidence in socioeconomically well-developed countries (except Japan), in accordance with known risk factors and national actions for early detection. Lower rates of incidence were reported in Africa and Asia, but with an increasing trend. A later study that analyzed the rise of the global burden of breast cancer showed variability among countries, for example, increasing incidence and mortality in China and South Korea, but decreasing trends in the United States [4]. In a comparison of differences in breast cancer mortality rates among 35 European countries, a World Health Organization database [5] found higher mortality rates in Eastern European countries.

Differences in mortality rates have also been reported in national surveys. In the United States, a decline has been reported for all women since 1990, but mortality rates are stable for American Indian/Alaskan Native women [1]. Cancers with the worst prognosis have been detected in non-Hispanic black women [6]. Similar trends have been reported from Sao Paolo, Brazil. Those trends show a higher prevalence of breast cancer death in white compared to black women, but with a decreasing trend among white women and an increasing trend among black women [7].

Similar to other Western countries, breast cancer is the most common malignancy among women in Israel [8]. The incidence of breast cancer in Israel follows world patterns, being highest among Jewish women of European (Ashkenazi) origin and lowest among women of North African and Asian origin [8]. Arab women present the lowest incidence [9]. In the last three decades, the incidence of breast cancer in Israel has increased more rapidly among Arab women [9] than among Jewish women. Adjusted incidence among Arab women rose from 14.1 per 100,000 1979–1981 to 42.6 per 100,000 in 2000–2002, while in Jewish women incidence rose from 45.7 to 71 per 100,000, respectively [9].

The incidence of invasive breast cancer during 1996–2001 compared to 2001–2004 revealed a stable trend among Jewish women with minor fluctuations, while a decreasing trend has been recorded since 2015 [10]. During these same time periods, a constant increasing trend was recorded for Arab women. When examining age at diagnosis in 2019, the median age among Jewish women was 63.6 years, while the median age among Arab women was 54.7 years. In contrast to the data for invasive breast cancer, the incidence of breast cancer in situ was higher among Jewish women than among Arab women. As a

result, the 5-year survival rate was higher among Jewish women than among Arab women but showed a trend of improvement over time for both groups. A comparison between the years 1996–2001 and 2002–2007 showed an improvement in survival rate from 84.3 to 86.3% for Jewish women, and from 73.7 to 82.1% for Arab women.

Development of breast cancer is associated with several modifiable and non-modifiable risk factors. Modifiable factors include obesity in the postmenopausal period [11], use of hormone replacement therapy (HRT), and smoking habits [12]. Non-modifiable factors included older age [13,14], family history [15], genetic mutations, and atypical hyperplasia [16]. Reproductive patterns, determined by younger age at menarche [15] and older age at menopause [16], are some of the main risk factors for breast cancer. Use of hormones, in particular exposure to sex hormones [17], is also considered a risk factor for breast cancer. Throughout adult life, women can be exposed to several kinds of hormonal medications, from oral contraceptives (OCCP) to prevent pregnancy, to regimens of hormonal medications for treatment of infertility, to HRT. The association between exposure to hormonal medications and breast cancer is not uniform; it depends on the type of medication, but even so, there is no consensus [18-21].

In Israel, screening for breast cancer by mammography is recommended for every woman aged 50 years and older at 2-year intervals. Screening mammography is included in the services provided by Israel's health maintenance organizations (HMOs) free of charge.

We explored differences in breast cancer diagnosis between Arab and Jewish women with respect to age at diagnosis, exposure to hormonal treatment, and other risk factors.

## PATIENTS AND METHODS

Israel operates a national health insurance scheme, and members are registered with a personal family physician. In the northern region of Israel, over 70% of the residents are members of Clalit Health Services. Clalit operates an integrated electronic medical and administrative file for each patient, based on the International Classification of Diseases (9th Revision). Diagnoses are based on reports from family physicians, community-based specialists, and hospital discharge letters. Clalit also maintains a central registry for malignant diseases, updated according to the information in the central registry of the Ministry of Health.

Our retrospective study was based on data collected by Clalit. The women included in the study were diagnosed with breast cancer during the period 2004–2015 and entered the study in the year of diagnosis.

We compared Jewish and Arab women for risk factors of breast cancer. We used measurable risk factors available in the Clalit database: older age [11], smoking habits [12,16], and obesity at menopausal age [11]. The retrieved data included baseline sociodemographic data, date of birth, date of diagnosis of breast cancer, and ethnicity (Jewish or Arab). We also retrieved data on all types of hormonal medications used prior to the diagnosis of breast cancer. We included clinical information on smoking and obesity based on the date of inclusion in the Clalit registry of chronic diseases.

The association between the history of use of hormonal medications and breast cancer was analyzed by classifying the medications into groups according to their content and type of use: hormonal medications for treatment of infertility (in vitro fertilization or ovulation stimulants), OCCP, progestogens (medications containing progesterone), and HRT.

### STATISTICS

Statistical analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA). Characteristics of women with breast cancer and risk factors were reported as percentages (%). To determine the associations between ethnicity or age and risk factors, we used the chi-square test and calculated odds ratios (OR) and 95% confidence intervals (95%CI). Differences between ethnic groups with respect to age (as a continuous variable) were assessed using Student's *t*-test. *P*-value < 0.05 was considered statistically significant.

The research was approved by the Helsinki Committee of C;a;ot, number 0058-16-COM2.

## RESULTS

### DEMOGRAPHICS AND RISK FACTORS

During the study period, 243,502 women over the age of 18 years were under the care of physicians associated with Clalit in the northern district; 75% of them were Jews [Table 1]. We identified 2494 women diagnosed with breast cancer. The mean age at diagnosis of breast cancer was 55.5 ± 13.3 (range 18–94, median 55.9 years). Age at diagnosis was earlier among Arab women (51.0 ± 13.5 vs. 57.3 ± 12.8 respectively, $P < 0.0001$) [Table 1]. Accordingly, diagnosis before the age of 50 years was more prevalent among Arab women (44.7% vs. 26.7% respectively, $P < 0.0001$). The rate of obesity (body mass index [BMI] ≥ 30) was higher among Arab women (44.7% vs. 37.3%, $P = 0.002$), and more significant above the age of 50 years (59.0% vs. 42.4%, $P < 0.0001$). Smoking was more prevalent among Jewish women (16% vs. 4.3%, $P < 0.0001$) [Table 1].

### USE OF HORMONAL MEDICATIONS IN ARAB AND JEWISH WOMEN WITH BREAST CANCER

Use of any listed hormonal medication before the diagnosis of breast cancer was more frequent among Jewish than Arab women (37.9% vs. 29.2% respectively, $P < 0.0001$) [Table 2] with differences between the hormones [Table 2]. Similarly, the chance of previously using any hormonal medication was

**Table 1.** Demographic and health characteristics of the Arab and Jewish study participants, 504 have missing values for BMI and 441 for smoking

| | | Total (N=2494) | | Arab (n=712) | | Jewish (N=1782) | | *P*-value |
|---|---|---|---|---|---|---|---|---|
| | | N | % | n | % | N | % | |
| Age at diagnosis | < 50 years | 794 | 31.8 | 318 | 44.7 | 476 | 26.7 | < 0.0001 |
| | > 50 years | 1700 | 68.2 | 394 | 55.3 | 1306 | 73.3 | |
| BMI | < 30 | 1203 | 60.5 | 336 | 55.4 | 867 | 62.7 | 0.0022 |
| | 30 | 787 | 39.5 | 271 | 44.7 | 516 | 37.3 | |
| BMI at age ⩾ 50 years | < 30 | 747 | 53.5 | 140 | 41.0 | 607 | 57.6 | < 0.0001 |
| | ⩾ 30 | 649 | 56.5 | 202 | 59.0 | 447 | 42.4 | |
| Smoking | No | 1797 | 87.5 | 599 | 95.7 | 1198 | 84.0 | < 0.0001 |
| | Yes | 256 | 12.5 | 27 | 4.3 | 229 | 16.0 | |

BMI = body mass index

**Table 2.** Use of hormonal medications by Arab and Jewish women with breast cancer

| Hormonal medication used | | Total (N=2494) | | Arab (n=712) | | Jewish (n=1782) | | *P*-value |
|---|---|---|---|---|---|---|---|---|
| | | N | % | n | % | n | % | |
| Hormonal medications for treatment of infertility (in vitro fertilization or ovulation stimulants) | No | 2395 | 96.0 | 666 | 93.5 | 1729 | 97.0 | < 0.0001 |
| | Yes | 99 | 4.0 | 46 | 6.5 | 53 | 3.0 | |
| Hormone replacement therapy | No | 2073 | 83.1 | 650 | 91.3 | 1423 | 79.9 | < 0.0001 |
| | Yes | 421 | 16.9 | 62 | 8.7 | 359 | 20.1 | |
| Progestogens | No | 2118 | 84.9 | 566 | 79.5 | 1552 | 87.1 | <0.0001 |
| | Yes | 376 | 15.1 | 146 | 20.5 | 230 | 12.9 | |
| Oral combined contraceptive pills | No | 2206 | 88.5 | 669 | 94.0 | 1537 | 86.3 | 0.0001 |
| | Yes | 288 | 11.5 | 43 | 6.0 | 245 | 13.7 | |
| At least one of the above hormonal medications | No | 1611 | 64.6 | 504 | 70.8 | 1107 | 62.1 | < 0.0001 |
| | Yes | 883 | 35.4 | 208 | 29.2 | 675 | 37.9 | |

lower in Arab women (OR 0.6, 95%CI 0.6–0.8) with differences between the hormones [Table 2]. Compared to Jewish women, Arab women had a higher chance of using progestogens (OR 1.7, 95%CI 1.4–2.2) and hormonal medications for treatment of infertility (OR 2.3, 95%CI 1.5–3.4), and a lower chance of using OCCP (OR 0.4, 95%CI 0.3–0.6) and HRT (OR 0.4, 95%CI 0.3–0.5).

## DISCUSSION

In our study, we looked for differences in risk factors for breast cancer between Jewish and Arab women living in the same area in Israel. Arab women with breast cancer were younger than Jewish women, presenting diagnosis of cancer more commonly before the age of 50 years, in the pre-menopausal period and below the age for routine mammography screening. With respect to exposure to hormonal medications, Arab women had a higher chance of previous use of progestogens and hormonal medications for treatment of infertility and a lower chance of previous use of HRT and OCCP. Obesity was more prevalent among Arab women, being more pronounced at age 50 and older, while smoking was more prevalent among Jewish women.

Israel's population presents differences between Jewish and Arab women with respect to breast cancer epidemiology, with a rising trend of incidence among Arab women compared to Jewish women [9]. Our observation of higher rates of diagnosis of breast cancer and more aggressive characteristics among Arab compared to Jewish women, below the age of 50, is in accordance with a previous study by Zidan and colleagues [22]. Their research also took place in the north of Israel. The evidence from Israel is supported by a review by Chouchane et al. [23] on the increasing trend of breast cancer among Arab women globally.

Previous studies have indicated a possible contribution of the use of hormonal medications to breast cancer, with different conclusions related to the type of hormones. Specifically, HRT is one of the most recognized medications linked to breast cancer. The risk is mainly among current users and increases with time [18].

The issue of possible associations between hormonal medications for treatment of infertility and breast cancer was discussed in a systematic review and meta-analysis by Beebeejaun et al. [24]. Their study included 20 studies, nine of them retrospective. They determined that the value of these studies was very low due to serious risks of bias and indirectness. From the available study material, they concluded that there was no significant increase in the risk of breast cancer with use of any kind of ovarian stimulation hormones.

The use of oral contraceptives has been reported to increase the risk of breast cancer for up to 5 years after discontinuation of its use [20]. A Danish prospective cohort study reported that besides the increased risk of breast cancer associated with the use of combined oral contraceptives, the use of a progestin-only intrauterine device is also associated with higher risk of breast cancer [21]. In contrast, a systematic review of six articles published during 2000–2005 concluded that there was no increase in risk of breast cancer with the use of progestins, but the conclusions were limited by the small sample size used in some of the studies [20]. Apparently, the jury is still out on the issue of exposure to hormones and breast cancer. We have not found any data related to the use of hormonal medications, specifically among Arab women in Israel.

The results of our study indicate differences in exposure to hormonal medications between Arab and Jewish women. The scope of our study does not explain these differences. We suggest that the differences in breast cancer between Arab and Jewish women in Israel may be associated with the social changes being experienced by Arab women in Israel.

The rate of fertility in Israel is higher among Arab women than among Jewish women, with a decreasing trend among Arab women. The fertility rate among Arab women was 4.7 children per woman in 1995–1999 vs. 3.3 in 2015–2019, compared to 2.6 vs. 3.14, among Jewish women [25]. This decreasing trend in fertility rate may contribute to the rise in the risk of breast cancer and may be associated with increasing use of hormonal contraceptives. We do not have an explanation for the difference in use of progestogens in favor of Arab women.

The rate of smoking was higher in Jewish women while the rate of obesity was higher in Arab women, regardless of age at diagnosis. Obesity during menopause is a major risk factor for breast cancer [11].

The strength of the present study lies in its considerable sample size, using reliable data from the community. Due to high coverage of the population in the north by Clalit, the study sample represents a large proportion of the population living in this area. Data on the use of medications are very reliable and are based on purchases at Clalit-affiliated pharmacies at a reduced price.

Our study has several limitations due to its retrospective nature. The study is limited by data that were not available to us, such as a family history of breast cancer. This limitation prevented us from differentiating between women at various levels of risk. However, due to the low incidence of breast cancer in the Arab population, the lack of genetic information might not seriously limit the significance of our observation.

Due to a lack of data on births, we were also unable to evaluate the role of obstetric history with respect to the use of birth control medications and hormonal medications for treatment of infertility. We also could not analyze differences in the severity of the disease as this information is based on pathology data, which are not shared with the community.

Another limitation is the incompleteness of the data on BMI, which may limit our analysis related to obesity. Women may also consult or be cared for by private doctors; however, medications are regularly purchased at subsidized prices in Clalit-affiliated pharmacies.

## CONCLUSIONS

Our small-scale study reveals some evidence related to breast cancer in Arab and Jewish women. We collated data related to risk factors for Arab and Jewish women living in the same area and attended by the same health care provider. These data open the way for further questions on lifestyle, focusing on the approach to women's fertility and family planning using various medications.

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### References

1. Althuis MD, Dozier JM, Anderson WF, Devesa SS, Brinton LA. Global trends in breast cancer incidence and mortality 1973-1997. *Int J Epidemiol* 2005; 34 (2): 405-12.
2. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; 65 (2): 87-108.
3. Hortobagyi GN, de la Garza Salazar J, Pritchard K, et al; ABREAST Investigators. The global breast cancer burden: variations in epidemiology and survival. *Clin Breast Cancer* 2005; 6 (5): 391-401.
4. Lei S, Zheng R, Zhang S, et al. Global patterns of breast cancer incidence and mortality: A population-based cancer registry data analysis from 2000 to 2020. *Cancer Commun (Lond)* 2021; 41 (11): 1183-94.
5. Wojtyla C, Bertuccio P, Wojtyla A, La Vecchia C. European trends in breast cancer mortality, 1980-2017 and predictions to 2025. *Eur J Cancer* 2021; 152: 4-17.
6. Kohler BA, Sherman RL, Howlader N, et al. Annual Report to the Nation on the Status of Cancer, 1975-2011, Featuring Incidence of Breast Cancer Subtypes by Race/Ethnicity, Poverty, and State. *J Natl Cancer Inst* 2015; 107 (6): djv048.

7. Marcelino AC, Gozzi B, Cardoso-Filho C, Machado H, Zeferino LC, Vale DB. Race disparities in mortality by breast cancer from 2000 to 2017 in São Paulo, Brazil: a population-based retrospective study. *BMC Cancer* 2021; 21 (1): 998.
8. State of Israel, Ministry of Health. Cancer information page. [Available from https://www.health.gov.il/English/MinistryUnits/ICDC/Chronic_Diseases/Cancer/Pages/default.aspx].
9. Tarabeia J, Baron-Epel O, Barchana M, Liphshitz I, Ifrah A, Fishler Y, Green MS. A comparison of trends in incidence and mortality rates of breast cancer, incidence to mortality ratio and stage at diagnosis between Arab and Jewish women in Israel, 1979-2002. *Eur J Cancer Prev* 2007; 16 (1): 36-42.
10. State of Israel, Ministry of Health. Israel Center for Disease. Control Breast Cancer in Israel. Updated morbidity and mortality data. [Available from https//www.health.gov.il/PublicationsFiles/breast_cancer_october2022.pdf]. [Accessed October 2022]. [Hebrew].
11. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin* 2019; 69 (1): 7-34.
12. Gaudet MM, Gapstur SM, Sun J, Diver WR, Hannan LM, Thun MJ. Active smoking and breast cancer risk: original cohort data and meta-analysis. *J Natl Cancer Inst* 2013; 105 (8): 515-25.
13. Collaborative Group on Hormonal Factors in Breast Cancer. Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease. *Lancet* 2001; 358 (9291): 1389-99.
14. Morrow M, Schnitt SJ, Norton L. Current management of lesions associated with an increased risk of breast cancer. *Nat Rev Clin Oncol* 2015; 12 (4): 227-38.
15. Ritte R, Lukanova A, Tjønneland A, et al. Height, age at menarche and risk of hormone receptor-positive and -negative breast cancer: a cohort study. *Int J Cancer* 2013; 132 (11): 2619-29.
16. Collaborative Group on Hormonal Factors in Breast Cancer. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. *Lancet Oncol* 2012; 13 (11): 1141-51.
17. Rojas K, Stuckey A. Breast cancer epidemiology and risk factors. *Clin Obstet Gynecol* 2016; 59 (4): 651-72.
18. Beral V; Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2003; 362 (9382): 419-27.
19. Samson M, Porter N, Orekoya O, et al. Progestin and breast cancer risk: a systematic review. *Breast Cancer Res Treat* 2016; 155 (1): 3-12.
20. Del Pup L, Codacci-Pisanelli G, Peccatori F. Breast cancer risk of hormonal contraception: Counselling considering new evidence. *Crit Rev Oncol Hematol* 2019; 137: 123-30.
21. Mørch LS, Skovlund CW, Hannaford PC, Iversen L, Fielding S, Lidegaard Ø. Contemporary hormonal contraception and the risk of breast cancer. *N Engl J Med* 2017; 377 (23): 2228-39.
22. Zidan J, Sikorsky N, Basher W, Sharabi A, Friedman E, Steiner M. Differences in pathological and clinical features of breast cancer in Arab as compared to Jewish women in Northern Israel. *Int J Cancer* 2012; 131 (4): 924-9.
23. Chouchane L, Boussen H, Sastry KS. Breast cancer in Arab populations: molecular characteristics and disease management implications. *Lancet Oncol* 2013; 14 (10): e417-24.
24. Beebeejaun Y, Athithan A, Copeland TP, Kamath MS, Sarris I, Sunkara SK. Risk of breast cancer in women treated with ovarian stimulation drugs for infertility: a systematic review and meta-analysis. *Fertil Steril* 2021; 116 (1): 198-207.
25. Israel. Central Bureau of Statistics. Population and vital statistics, 1981. *Mon Bull Stat U N Stat Off* 1983; 34 (2 Suppl): 33-64. English, Hebrew.


**It is chiefly through books that we enjoy intercourse with superior minds.**
William Ellery Channing (1780–1842), English clergyman and writer

**In three words I can sum up everything I've learned about life: it goes on.**
Robert Frost (1874–1963), American poet

**Capsule**

## Randomized trial of early detection and treatment of postpartum hemorrhage

Delays in the detection or treatment of postpartum hemorrhage can result in complications or death. A blood-collection drape can help provide objective, accurate, and early diagnosis of postpartum hemorrhage, and delayed or inconsistent use of effective interventions may be addressed by a treatment bundle. **Gallos** et al. examined a total of 80 secondary-level hospitals across Kenya, Nigeria, South Africa, and Tanzania, in which 210,132 patients underwent vaginal delivery, and randomly assigned them to the intervention group or the usual-care group. Among hospitals and patients with data, a primary-outcome event occurred in 1.6% of the patients in the intervention group, compared with 4.3% of those in the usual-care group (risk ratio 0.40; 95% confidence interval [95%CI] 0.32–0.50, $P < 0.001$). Postpartum hemorrhage was detected in 93.1% of the patients in the intervention group and in 51.1% of those in the usual-care group (rate ratio 1.58. 95%CI 1.41–1.76), and the treatment bundle was used in 91.2% and 19.4%, respectively (rate ratio 4.94, 95%CI 3.88–6.28). Early detection of postpartum hemorrhage and use of bundled treatment led to a lower risk of the primary outcome, a composite of severe postpartum hemorrhage, laparotomy for bleeding, or death from bleeding, than usual care among patients having vaginal delivery.

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