Supplement 1

Indications for aromatase inhibitor therapy [4]

‘The clinic began using anastrozole, an aromatase inhibitor, combined in the pellet implant in 2008, initially to treat symptoms of hormone deficiency in estrogen receptor positive breast cancer survivors. The amount of anastrozole in each pellet implant is 4 mg combined with 60 mg of T, providing continuous and simultaneous release of both the T and anastrozole. A dose of 4 to 8 mg of anastrozole (1 or 2 T + A implants) has been shown to prevent elevation of estradiol in breast cancer survivors treated with subcutaneous T [20, 25]. Subsequently, beginning in 2010, women who presented with signs or symptoms of excess estrogen (e.g., breast pain, fluid retention, weight gain, anxiety, irritability), obesity, or increased risk for breast cancer, were treated with anastrozole in combination with T. It was also found that pre-menopausal patients with symptoms of excess estrogen including migraine headaches, dysfunctional uterine bleeding, endometriosis, uterine fibroids, breast pain, or severe premenstrual syndrome also benefited from the ‘low dose’ anastrozole (compared to 1 mg/day oral) delivered subcutaneously with T. T and T + A dosing is based on clinical history and symptoms, response to therapy, weight (BMI), amount of fatty tissue, and laboratory evaluation of hormone levels. There have been no adverse drug events related to subcutaneous anastrozole therapy. The amount of anastrozole released over 100 days is approximately 0.04–0.08 mg per day.’

Reference

1. Glaser RL, York AE, Dimitrakakis C (2019) Incidence of invasive breast cancer in women treated with testosterone implants: A prospective 10-year cohort study. BMC Cancer 19: 1271.

Supplement 2

Statistical methods

The incidence rates of invasive breast cancer (BCI) for the Dayton study are reported as an unadjusted, unweighted value of newly diagnosed cases. The Dayton BCI was calculated as described by equation (1), where N is the number of breast cancer cases observed in the Dayton study, and y_i the person-time observed for age group i (see age group in table 1). Person-year is the period from the first implant date until the following observed event in the 'at risk' population: date of cancer registration, date of death, 240 days after the last pellet insert, or the set date of March 2023, whichever occurred first. Unlike pills and topical therapy, 240 days was chosen considering that subcutaneous implants are long-acting (sustained release) and the incidence of breast cancer was reported for a predetermined time frame of 240 days post-implantation or 2.5 times the average length of clinical efficacy of 96 days [1,2] The person-years (p-y) were calculated by dividing person-days by 365.25. The incidence of breast cancer was calculated per 100,000 p-y so that our results could be compared to age-matched SEER breast cancer incidence rates and historical studies.

$$(1)\quad \mu_{Dayton} = \frac{100{,}000 \times N}{\Sigma\, y_i}$$

The standard deviation of the observed Dayton incidence rate was calculated assuming the number of cancers follows a Poisson distribution so that, N is the number of breast cancer cases and Y_i the person-time observed for age group i (Equation 2).

$$(2)\ SD(\mu_{Dayton}) = \frac{100{,}000 \times N^{.5}}{\Sigma\, y_i}$$

The observed breast cancer incidence rates for the Dayton study patients were compared to the expected (adjusted) SEER breast cancer incidence rates calculated from the age composition of Dayton study patients and the published SEER age-grouped breast cancer incidence rates (Table 1) [3]. The delay-adjusted breast cancer incidence rates were collected using the SEER*StatApplication software (v. 9.0 30.0) (www.seer.cancer.gov/seerstat). The ‘expected incidence’ (Equation 3) is a weighted sum of the SEER incidence rates (s_i) with the weights corresponding to the proportion (p_i) of the Dayton study patients’ person-years (p-y) in each of the SEER age groups per sum of person-year of all age groups.

$$(3)\ \mu_{SEER} = \sum s_i\ p_i$$

The variance of the expected incidence rate (SEER) was estimated using weighted sum of the estimates of SEER incidence SDs (table 1) and the corresponding proportion (p_i) of the Dayton study patients' person-years (p-y) in each of the SEER age groups (Equation 4)

$$(4)\ Var_{(\mu_{SEER})} = \sum (SD_i \times p_i)^2$$

Confidence intervals of the Dayton incidence rates based on the whole sample were computed from the Poisson assumption using the R function for the Poisson exact test based on procedures in [4], Chapter 6. Tests of the null hypothesis that Dayton and expected SEER rates were the same were carried out with the same procedure. The significance level of 0.05 was established for all inferential statistics.

A comparison of body mass index (BMI) between eligible patients with cancer diagnosis and patients without cancer. The Shapiro-Wilk normality test was applied, followed by Wilcoxon rank sum test. All statistics were performed in RStudio version 1.4 [5].

Database name: Incidence - SEER Research Limited-Field Data with Delay-Adjustment, 22 Registries, Malignant Only, Nov 2022 Sub (2000-2020) - Linked To County Attributes - Time Dependent (1990-2021) Income/Rurality, 1969-2021 Counties

Incidence - SEER Research Limited-Field Data with Delay-Adjustment Nov 2022 Sub (2000-2020)		
	BCI	SD
Ages 15-19	0.163	0.066
Ages 20-24	1.559	0.131
Ages 25-29	9.265	0.291
Ages 30-34	27.919	0.915
Ages 35-39	61.554	1.443
Ages 40-44	126.865	3.122
Ages 45-49	195.414	4.511
Ages 50-54	231.735	7.195
Ages 55-59	269.096	6.493
Ages 60-64	346.127	9.462
Ages 65-69	432.721	10.364
Ages 70-74	467.814	14.110
Ages 75-79	466.629	9.784
Ages 80-84	428.639	11.151
Ages 85+	343.785	11.887

Table 1: Breast cancer incidence rates (BCI) per 100,000 person-year and standard deviation (SD) as reported by SEER.

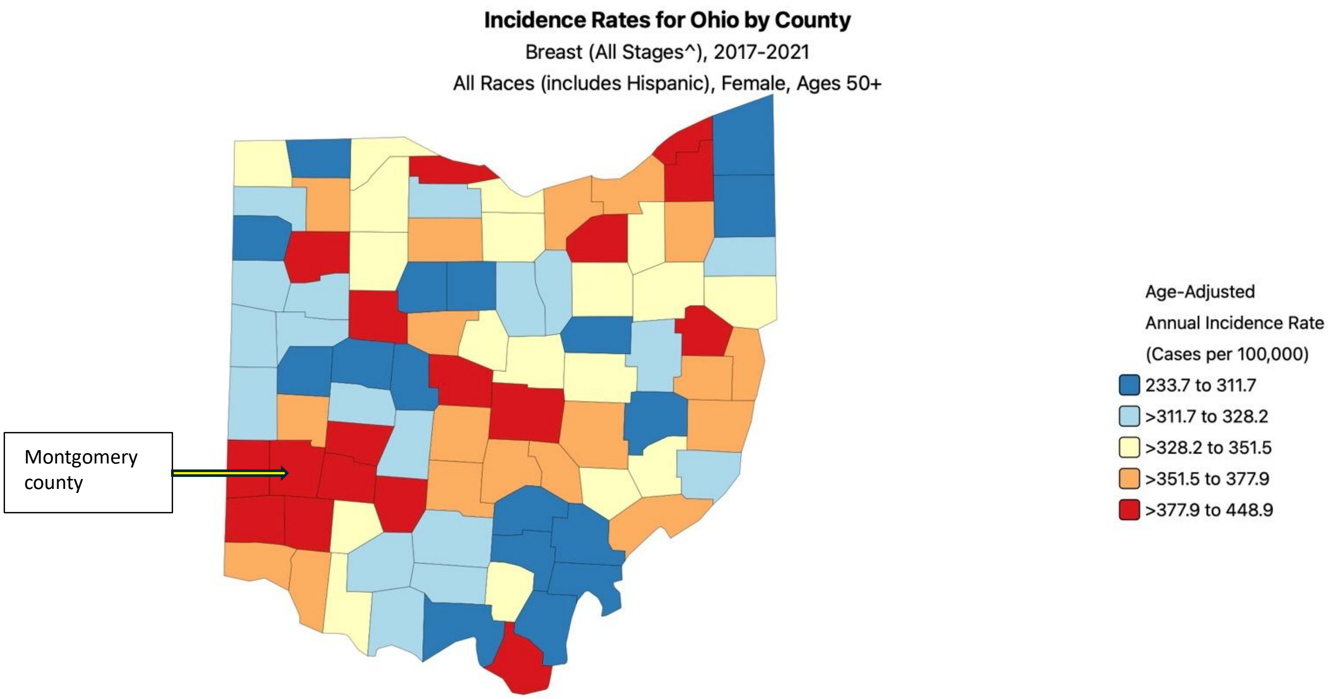
References

1. Glaser RL, Dimitrakakis C (2013) Reduced breast cancer incidence in women treated with subcutaneous testosterone, or testosterone with anastrozole: A prospective, observational study. Maturitas 76: 342-349.
2. Glaser R, York AE, Dimitrakakis C (2019) Incidence of invasive breast cancer in women treated with testosterone implants: a prospective 10-year cohort study. BMC Cancer 19: 1271.
3. National Program of Cancer Registries and Surveillance, Epidemiology, and End Results SEER (2022) United States Department of Health and Human Services, Centers for Disease Control and Prevention.

4. Feller WF (1950) An Introduction to Probability Theory and its Applications. Volume 1. Wiley.
5. RStudio Team (2020) RStudio: integrated development for R.

Supplement 3

State cancer incidence map – location and contamination aquifer (GMVBA)

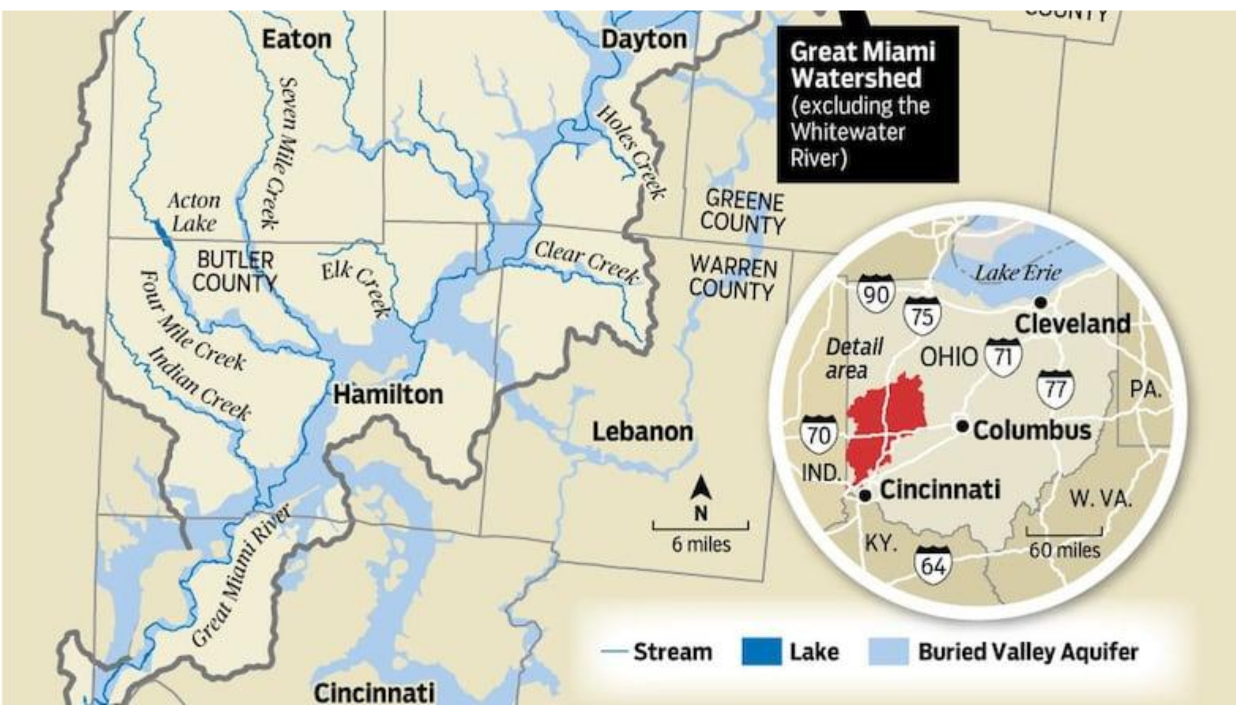


https://statecancerprofiles.cancer.gov/map/map.withimage.php?39&county&136&055&00&2&01&0&1&5&0#results

Location: Great Miami Buried Valley Aquifer (federally designated – Sole Source Aquifer)

https://www.daytondailynews.com/news/voices-how-toxic-industrial-spills-have-contaminated-our-groundwater/NUIMSH4YIVFK7KBFGA2XAY7NIM/

VOICES: How toxic industrial spills have contaminated our groundwater



By Abinash Agrawal

Aug 1, 2021

The Great Miami Buried Valley Aquifer (GMBVA) system is the city of Dayton's drinking water source. The aquifer can be described as a large network of underground water-bearing sediment deposit, which formed about 11,000 years ago. The GMBVA system is situated at shallow depth, and has a high overall capacity to supply drinking water upon pumping.

The GMBVA is recognized as a *Sole Source Aquifer* by the United States Environmental Protection Agency (USEPA). This designation applies only to aquifers serving as the sole or principal source of drinking water for the local area and which, if contaminated, would create a significant hazard to public health. Due to its shallow depth (close proximity to the ground surface), and the presence of a relatively thin protective sediment cover, the Ohio EPA has found the GMBVA system to be under the influence of surface water by recharge that makes it susceptible to contamination.

The specific VOCs found at the above sites are Trichloroethene (TCE) and Tetrachloroethene (PCE), and also their natural byproducts. TCE and PCE are legacy chemicals that were used in the U.S. in a variety of industrial applications for decades, but have been phased out. Since TCE and PCE do not breakdown easily in the environment, their contamination of the aquifer at the Superfund sites is mainly due to past spills as well as disposal practices. TCE and PCE are highly toxic and their level in the drinking water should not exceed above 5 micrograms per liter (or 5 parts per billion).

Coincidentally, the Behr Dayton Thermal VOC plume, North Sanitary Landfill, and Valley Pike VOC sites are all situated in close proximity to the two well fields from where drinking water is pumped out and then treated before supplying to the consumers. However, considerable scientific innovations now allow us to treat the contaminated zones of the aquifer directly and quickly by 'bioremediation' that employs native bacteria to convert the highly toxic TCE and PCE into benign byproducts cost effectively. A vigorous oversight is needed to destroy chlorinated solvents remaining areas of contaminated aquifer to protect drinking water quality.

The extensive aquifer contamination at the Valley Pike superfund site comes from decades of manufacturing activities that utilized TCE and PCE. The site was discovered in 2013 and then added to the Superfund program in 2016 due to the most serious and uncontrolled nature of the contamination at the site. The contaminated groundwater plume at the Valley Pike site begins at the manufacturing facility and flows to the southwest, which has affected hundreds of area residents due to entry of toxic vapors inside their homes.

Since September 2019, the Valley Pike site is going through an in-depth remedial investigation to better define the contamination and develop strategies for aquifer clean-up in order to protect the community health. The TCE and PCE liquid contamination at the site appears to have penetrated deep into the ground underneath affecting the aquifer. A dual approach will be needed to arrest further spread of toxic vapor as well as treatment of the contaminated groundwater plume in the short term to reduce the risk of human exposure. In addition, a strategy to destroy the VOCs in the source zone by injection of amendments into the subsurface may be appropriate.

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