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Why uterine cancer should be a WTC-certified condition

Uterine cancer: a brief overview of occurrence and risk factors

In the United States, cancer of the uterine corpus is the most common cancer of the female reproductive organs. In the US there are about 65,620 annual uterine cancer diagnosis and 12,590 deaths. Most diagnoses are endometrial cancer but about 10% uterine sarcomas.¹ Endometrial cancer has two general forms. Type I is a hormone-dependent cancer and tends to develop in women soon after menopause. The primary risk factor is exposure to either exogenous (e.g. HRT) or endogenous (chronic anovulation, null parity) unopposed estrogens. Other risk factors include obesity, high blood pressure, and genetics. The role of smoking is

¹ <https://www.cancer.org/cancer/endometrial-cancer/about/key-statistics.html>

unclear with some studies showing no contribution and others finding that smoking is associated with lower rates of Type I endometrial cancer. This later finding may be attributable to uncontrolled confounding for lower body mass index (BMI) associated with smoking. While the risk factors for Type II endometrial carcinomas are less well-defined, the patient profile is distinct from Type I. Type II endometrial cancer is more common among older women with a normal BMI who, have not been exposed to exogenous unopposed estrogens. Type II is also associated with multiparity and a higher incidence have been observed among African American women. Type II tumors are generally more aggressive with a poorer prognosis.² Historically, environmental factors have been considered to have little influence on the risk of endometrial cancer. However, in recent years, there is a growing focus on the possible role of endocrine disrupting chemicals (EDCs) in increasing the risk of hormone-related tumors, including endometrial cancer. [EDCs are defined by the World Health Organization (WHO), as “an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations.”³

Why uterine cancer should be a WTC-certified condition

In 2019, the CDC WTC-HP reviewed a petition filed on April 3 of that year to add endometrial cancer to the list of certifiable WTC-related conditions. The petition was denied based on: (1) lack of a proposed mechanism for carcinogenesis; (2) lack of coherence of evidence; (3) lack of observed excess of endometrial cancer among WTC-exposed populations compared to the general population; and, (4) lack of a dose-response relationship with WTC exposure.⁴

The mechanistic review and consideration of the coherence of evidence failed to consider the possible contribution of EDCs to uterine cancer incidence. Approximately 800 chemicals are known or suspected to have the potential to function as EDCs. This is a heterogeneous group of chemicals, many of which have been identified in the WTC dusts including some persistent organic pollutants such as polychlorinated dibenzo-para-dioxins and polychlorinated dibenzofurans (PCDD/Fs) and other industrial substances such as phthalates and per- and polyfluoroalkyl substances (PFAS).^{5,6} The potential role of EDCs in carcinogenesis of endometrial cancer is an emerging area of research and is generally focused on environmental epigenetics. For example, dysregulation of miRNA expression has been implicated in estrogen-related diseases, including endometrial cancer. Type I endometrial cancers are estrogen-dependent, as such, it is reasonable to expect that the estrogenic action of EDCs can influence its genesis through dysregulation of miRNA expression, as well as other pathways.⁷ Two recent reviews concluded that while additional studies are needed to clarify mechanisms, the carcinogenic effects of EDCs are indeed plausible.^{7,8}

² <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3699726/>

³ https://apps.who.int/iris/bitstream/handle/10665/78102/WHO_HSE_PHE_IHE_2013.1_eng.pdf?sequence=1

⁴ <https://www.federalregister.gov/documents/2019/09/24/2019-20364/world-trade-center-health-program-petition-023-uterine-cancer-including-endometrial-cancer-finding>

⁵ Lioy PJ, Weisel CP, Millette JR, et al. Characterization of the dust/smoke aerosol that settled east of the World Trade Center (WTC) in lower Manhattan after the collapse of the WTC 11 September 2001. *Environ Health Perspect*. 2002;110(7):703-714

⁶ Spratlen MJ, Perera FP, Lederman SA, Robinson M, Kannan K, Trasande L, Herbstman J. Cord blood perfluoroalkyl substances in mothers exposed to the World Trade Center disaster during pregnancy. *Environ Pollut*. 2019 Mar;246:482-490

⁷ Mallozzi M, Leone C, Manurita F, Bellati F, Caserta D. Endocrine Disrupting Chemicals and Endometrial Cancer: An Overview of Recent Laboratory Evidence and Epidemiological Studies. *International journal of environmental research and public health*. 2017;14(3).

⁸ La Merrill M. A. VLN, Smith M.T., Goodson W., Browne P., Patisaul H.B., Guyton K.Z., Kortenkamp A., Cogliano V.J., Woodruff T.J., Rieswijk L., Sone H., Korach K.S., Gore A.C., Zeise L., Zoeller R.T. Consensus on the key characteristics of endocrine-disrupting chemicals as a basis for hazard identification. *Nat Rev Endocrinol*. 2020;16(1):13.

As well, the first three of the criteria seem an unreasonably high bar, as they are not met for the vast majority of WTC-covered cancers. The review of the petition was particularly focused on whether there is a demonstrated excess of endometrial cancer and a direct link with WTC exposure. Few covered cancers currently meet this criterion.⁹ As well, the number of exposed and monitored women is relatively small in the two WTC-HP cohorts with the occupational WTC-exposure (14% of the General Responder Cohort and <1% of FDNY are female), so there is limited statistical power to observe excess cancer incidence. This is particularly an issue for the less common, and more aggressive Type II form of endometrial cancer.

As such, endometrial cancer should be reconsidered as a potential WTC-certified condition, and should: (1) consider the possible role of EDCs in carcinogenesis or promotion of endocrine-driven endometrial cancer, and (2) using the same evaluation criteria that has been applied to other solid tumors.

⁹ Boffetta P, Zeig-Owens R, Wallenstein S, et al. Cancer in World Trade Center responders: Findings from multiple cohorts and options for future study. *American journal of industrial medicine*. 2016;59(2):96-105