



Toward Understanding the Etiology of Male Breast Cancer: An Ongoing Research Challenge

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Male breast cancer is rare and accounts for less than 1% of all breast cancers, with an estimated 2650 new cases in the United States in 2021, compared with 281 550 cases for women (1). Despite increasing male breast cancer incidence rates worldwide over the past 3 decades (2), the etiology, prognosis, and treatment of male breast cancer is not well understood, as there are limited population-based studies and clinical trials focused on male breast cancer. Moreover, most treatment and clinical management guidelines for male breast cancer are based on studies of female breast cancer, even though men with breast cancer are older at diagnosis, are primarily diagnosed with hormone receptor-positive tumors, and have different hormonal profiles than females (3). Unlike female breast cancer risk factors that have been extensively studied, elucidating the role of different hormonal, genetic, and lifestyle factors for male breast cancer has been challenging, because of the rarity of the disease.

Obesity has been of particular interest in male breast cancer given its association with high estrogen levels, the hormonal activity of adipose tissue, and the established association of obesity with elevated risk of female postmenopausal breast cancer (4,5). Moreover, there is evidence that the rising rates of male obesity and increasing incidence of male breast cancer show parallel trends (6), although it is unclear if the two are linked. In female breast cancer, there is strong evidence that higher body mass index (BMI) and greater central adiposity are associated with increased risk of postmenopausal breast cancer, with heterogeneity by breast cancer subtype and underlying familial risk (5,7-9). In contrast, the evidence for obesity and male breast cancer is very limited but, based on smaller studies that examined BMI, not central adiposity or the associations by tumor subtype.

In this issue of the Journal, Swerdlow and colleagues (10) present evidence based on 1998 male breast cancer cases and 1597 controls that greater BMI and abdominal obesity are associated with increased risk of breast cancer in men. Considering the sparse evidence highlighted above, these are important and novel findings that leverage data from a large British population-based case-control study over a 12-year period, representing one of the largest and

most detailed studies examining this association to date. The authors report a statistically significant elevated risk of male breast cancer for increasing BMI at ages 20, 40, and 60 years (odds ratio [OR] = 1.07, 1.11, and 1.14 per 2-unit increase, respectively). They also report an association with increasing waist-to-height ratio at 5 years before interview (OR per 0.02-unit increase = 1.12, 95% confidence interval [CI] = 1.08 to 1.15). Notably, no previous study has examined the association of central obesity and male breast cancer. Overall, Swerdlow et al. (10) make a unique contribution to the literature with this analysis by examining the associations with BMI and central obesity at different ages.

The findings of the study are novel; however, some of the analyses are not easy to interpret. For example, the authors did not use World Health Organization BMI categories, which they suggest is because of small sample size in some categories in their study. Moreover, including recent BMI (ie, measured close to the diagnosis) would have been valuable for comparing against the only other large study examining this association, the Male Breast Cancer Pooling Project, which includes 2405 cases of male breast cancer and 52 013 controls from 11 case-control studies and 10 cohorts, and found that recent rather than distant BMI was a strong predictor (4). The pooling project reported a 19% increased risk per 5-unit increase in BMI (OR = 1.19, 95% CI = 1.1 to 1.3) and a 35% statistically significantly increased risk for obese men (BMI \geq 30 kg/m²) compared with normal weight men (BMI = 18.5-24.9 kg/m²) (4). Generally consistent with this information, Swerdlow et al. (10) found that recent waist-to-height ratio was a stronger risk factor than that at age 20 years.

It should be noted that, although the study by Swerdlow and colleagues (10) was one of the largest studies examining these associations to date, their study population was primarily comprised of White men (94% of cases and 98% of controls). As such, these findings may not be generalizable to other racial and ethnic groups, which may have different rates of obesity and other social and environmental factors that may be associated with cancer risk as well as different patterns of breast cancer subtypes. Considerably higher incidence rates have been reported in

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Black men compared with White men for all subtypes of breast cancer (11). Moreover, Black men experience worse overall survival following breast cancer diagnosis compared with White men, even after accounting for age and tumor characteristics (eg, stage, grade, estrogen receptor status) (12). Future studies aiming to understand the epidemiology of male breast cancer would greatly benefit from the inclusion of diverse populations to evaluate cancer disparities in incidence and survival, as well as potential differences in the survivorship experience.

In summary, findings from the study by Swerdlow and colleagues (10) provide additional evidence of the detrimental role of obesity and central obesity on breast cancer risk and warrant further studies. Ideally, future research efforts examining the association of obesity and male breast cancer should use a prospective design; include a diverse population of men, particularly Black men, and sufficient sample size to classify men according to clinically meaningful BMI categories; evaluate risk by tumor subtypes; and conduct anthropometric measurements to be able to characterize body fat distribution and body composition. However, this will continue to be challenging and will require a large multisite consortium. Meanwhile, the study by Swerdlow et al. contributes to the literature of a rare and challenging cancer to study in both epidemiologic studies and clinical trials and has important implications for male breast cancer risk estimation and prevention. Importantly, obesity is a risk factor for several chronic diseases in men and women, including several cancers, cardiovascular diseases, hypertension, and diabetes (13). Therefore, interventions aimed at obesity prevention and control will have broad public health implications in terms of reduced disease burden.

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References

1. Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2021. *CA A Cancer J Clin*. 2021;71(1):7–33.
2. Chen Z, Xu L, Shi W, et al. Trends of female and male breast cancer incidence at the global, regional, and national levels, 1990–2017. *Breast Cancer Res Treat*. 2020;180(2):481–490.
3. Giordano SH. Breast cancer in men. *N Engl J Med*. 2018;378(24):2311–2320.
4. Brinton LA, Cook MB, McCormack V, et al.; for the European Rare Cancer Study Group. Anthropometric and hormonal risk factors for male breast cancer: male breast cancer pooling project results. *J Natl Cancer Inst*. 2014;106(3):dj465.
5. World Cancer Research Fund–American Institute for Cancer Research. Continuous Update Project Expert Report 2018: Diet, nutrition, physical activity, and breast cancer. <http://dietandcancerreport.org/>. Published May 2018. Accessed July 15, 2021.
6. Humphries MP, Jordan VC, Speirs V. Obesity and male breast cancer: provocative parallels? *BMC Med*. 2015;13(1):134.
7. Smith SG, Sestak I, Morris MA, et al. The impact of body mass index on breast cancer incidence among women at increased risk: an observational study from the International Breast Intervention Studies. *Breast Cancer Res Treat*. 2021;188(1):215–223.
8. Hopper JL, Dite GS, MacInnis RJ, et al.; for the kConFab Investigators. Age-specific breast cancer risk by body mass index and familial risk: prospective family study cohort (ProF-SC). *Breast Cancer Res*. 2018;20(1):132.
9. Lauby-Secretan B, Scoccianti C, Loomis D, et al.; for the International Agency for Research on Cancer Handbook Working Group. Body fatness and cancer-viewpoint of the IARC working group. *N Engl J Med*. 2016;375(8):794–798.
10. Swerdlow AJ, Bruce C, Cooke R, et al. Obesity and breast cancer risk in men: national case-control study in England and Wales. *JNCI Cancer Spectr*. 2021. doi: 10.1093/jncics/pkab078.
11. Sung H, DeSantis C, Jemal A. Subtype-specific breast cancer incidence rates in Black versus White men in the United States. *JNCI Cancer Spectr*. 2020;4(1):pkz091.
12. Sun HF, Zhao Y, Gao SP, et al. Clinicopathological characteristics and survival outcomes of male breast cancer according to race: a SEER population-based study. *Oncotarget*. 2017;8(41):69680–69690.
13. Guh DP, Zhang W, Bansback N, et al. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. *BMC Public Health*. 2009;9:88.