# Prospective Evaluation of Risk Factors for Male Breast Cancer 

Louise A. Brinton, Douglas A. Richesson, Gretchen L. Gierach, James V. Lacey Jr, Yikyung Park, Albert R. Hollenbeck, Arthur Schatzkin


#### Abstract

Most risk factors for male breast cancer have been derived from retrospective studies that may reflect selective recall. In the prospective National Institutes of HealthAARP Diet and Health Study, we studied 324920 men, among whom 121 developed breast cancer. Men who reported a first-degree relative with breast cancer had an increased risk of breast cancer (relative risk $[R R]=1.92,95 \%$ confidence interval $[C I]=$ 1.19 to 3.09). Among the medical conditions examined, a new finding emerged regarding increased male breast cancer risk associated with a history of a bone fracture ( $R R=\mathbf{2 . 2 0}, \mathbf{9 5 \%} \mathbf{C l}=1.24$ to $\mathbf{3 . 9 1}$ ). Obesity was positively related to risk ( $\mathbf{R R}=$ $1.79,95 \% \mathrm{Cl}=1.10$ to 2.91 , for body mass indices of $\geq 30 \mathrm{vs}<\mathbf{2 5} \mathrm{kg} / \mathrm{m}^{2}$ ) and physical activity inversely related, even after adjustment for body mass index. Smokers were at somewhat elevated risk, although trends with smoking characteristics were inconsistent. Alcohol consumption was not related to risk. The identified risk factors show some commonalities with female breast cancer and indicate the importance of hormonal mechanisms. Differences in risk factors may reflect unique mechanisms associated with androgens and their ratio to bioavailable estrogens.


J Natl Cancer Inst 2008;100:1477-1481

Male breast cancer is uncommon, accounting for only $0.7 \%$ of all breast cancers (1). It is dissimilar to female breast cancer, in that incidence rates are higher among African American men than white men and continue rising in men aged 55 years or older, resulting in a late average age at onset $(2,3)$. Although numerous investigations emphasize familial or genetic associations, less is known regarding environmental effects. Reports of increased risks of male breast cancer among atomic bomb survivors (4) and individuals who have received medical irradiation (5-7) or had occupational exposure to electromagnetic fields (8-10) support a role for ionizing radiation. Hormonal factors have also been implicated, through relationships with obesity $(6,11-14)$, physical inactivity $(12,13)$, alcohol consumption $(7,15)$, and use of exogenous androgens $(16,17)$ or estrogens $(18,19)$.

Given that many of the identified risk factors may reflect selective recall after disease onset, we prospectively evaluated risk factors within the large National Institutes of Health-AARP (formerly known as the American Association of Retired Persons) Diet and Health Study. This cohort was established in 1995 and

1996, when a detailed questionnaire was sent to 3.5 million members aged $50-71$ years (20), with 567169 (16.2\%) satisfactorily completing it. After various exclusions (deaths or having moved, $\mathrm{n}=590$; proxy respondents, $\mathrm{n}=15760$; withdrawals, $\mathrm{n}=6$; duplicate questionnaires, $\mathrm{n}=179$; women, $\mathrm{n}=225468$; and previous breast cancers, $\mathrm{n}=246$ ), 324920 study subjects remained. Subjects were followed annually for changes of address. Incident cancers were identified by linkage to 11 state cancer registries, and deaths were identified through the National Death Index. From baseline through December 31, 2003, 2313988 person-years were contributed and 121 men (median age $=68$ years) developed breast cancer (nine with in situ disease, 107 with invasive breast cancer, and five with missing stage). The Special Studies Institutional Review Board of the National Cancer Institute approved this study, and written informed consent was obtained from study participants.

Using multivariable Cox proportional hazards regression to estimate relative risks (RRs) and 95\% confidence intervals (CIs), we found an increased risk associated with the reporting of a first-degree relative with breast cancer $(\mathrm{RR}=1.92,95 \% \mathrm{CI}=1.19$ to
3.09) (Table 1). Risk was particularly elevated for individuals with an affected sister $(\mathrm{RR}=2.25,95 \% \mathrm{CI}=1.13$ to 4.47$)$, possibly reflecting the influence of shared genetic and environmental risk factors. A particularly enhanced risk was found for those with both an affected mother and an affected sister ( $\mathrm{RR}=9.73,95 \% \mathrm{CI}=3.96$ to $23.96, \mathrm{n}=5$ ).

Our results agree with others who have identified familial relationships for male breast cancers ( $6,7,11,13,21-23$ ), including one report showing an increased risk with multiple affected relatives (23). These associations mirror patterns observed for female breast cancer; however, the role of specific genetic mutations (particularly in BRCA2) appears to differ for the two diseases $(24,25)$.

In both females and males, genetic mutations appear to explain only a small proportion of disease occurrence, leading to interest in other contributory factors, including various medical conditions. Of note is a very strong relationship for male breast cancer ( 50 -fold increase) that has been observed with Klinefelter syndrome $(26,27)$, a condition associated with increased gonadotropin and decreased androgen levels, normal estrogen levels, and therefore a high ratio of estrogen to androgen $(14,28,29)$. Studies have indicated relationships with other chronic conditions, including liver cirrhosis $(22,30)$, hyperthyroidism (22), gallstones (22), and diabetes $(11,14)$, albeit usually on the basis of small numbers. We did not have information on liver or thyroid diseases, but we observed no increased risk related to diabetes, gallstones, heart diseases, or colorectal polyps.

Somewhat surprisingly, we observed a statistically significant increased risk associated with bone fractures occurring after age

[^0]
## CONTEXT AND CAVEATS

## Prior knowledge

Many risk factors for male breast cancer have been identified in studies that may suffer from the selective recall of participants.

## Study design

Prospective cohort study of more than 300000 men in the National Institutes of Health-AARP Diet and Health Study, who submitted a completed questionnaire and of whom 121 developed breast cancer.

## Contribution

Having a first-degree relative with breast cancer, having a bone fracture after the age of 45 years, and being obese were associated with an increased risk of male breast cancer. Physical activity, after adjustment for body mass index, was inversely related to risk. Alcohol consumption was not related to risk.

## Implications

Commonalities between risk factors for male and female breast cancer indicate that hormonal mechanisms may be important, whereas differences may reflect unique mechanisms that may be associated with androgens. Because of the small number of patients with male breast cancer in this and other studies, however, risk factors for male breast cancer should be investigated further in pooled analyses across many studies.

## Limitations

This study had relatively few participants who developed male breast cancer, which limited its power to detect rare exposures. The generalizability of the results is unclear because the findings were based on selfreported information and the response rate to the questionnaire was low.

From the Editors

45 years $(\mathrm{RR}=2.20,95 \% \mathrm{CI}=1.24$ to 3.91). This new finding was unexpected because breast cancers are less likely to occur among women with fractures (31) and such fractures have generally been attributed to low estrogen levels. Although estrogens are important for bone maintenance in males $(32,33)$, gonadal insufficiency and low testosterone levels also contribute to bone density and osteoporosis (34). Given decreasing testosterone levels with age, bone fractures may relate to

Table 1. Associations of male breast cancer with family and medical histories: National Institutes of Health-AARP Diet and Health Study*

| Characteristic | No. of patients $(\mathrm{n}=121)$ | No. of person-years $\dagger$ | RR $\ddagger$ (95\% CI) |
| :---: | :---: | :---: | :---: |
| Family history |  |  |  |
| Any cancer |  |  |  |
| No | 40 | 1091455 | 1.00 (referent) |
| Yes | 72 | 1108921 | 1.74 (1.19 to 2.57) |
| Unknown | 9 | 113613 | 1.84 (0.88 to 3.84) |
| Breast cancer |  |  |  |
| No | 91 | 1966058 | 1.00 (referent) |
| Yes | 21 | 234318 | 1.92 (1.19 to 3.09) |
| Mother alone | 7 | 135964 | 1.15 (0.53 to 2.49) |
| Sister alone | 9 | 81512 | 2.25 (1.13 to 4.47) |
| Mother and sister | 5 | 11045 | 9.73 (3.96 to 23.96) |
| Unknown | 9 | 113613 | 1.47 (0.73 to 2.96) |
| Other cancers |  |  |  |
| No | 67 | 1442163 | 1.00 (referent) |
| Yes | 45 | 758212 | 1.26 (0.86 to 1.83) |
| Unknown | 9 | 113613 | 1.46 (0.72 to 2.96) |
| Prostate cancer |  |  |  |
| No | 97 | 1998520 | 1.00 (referent) |
| Yes | 15 | 201855 | 1.51 (0.88 to 2.61) |
| Unknown | 9 | 113613 | 1.40 (0.70 to 2.81) |
| Diagnosis (ever) |  |  |  |
| Gallbladder stones or disease |  |  |  |
| No | 112 | 2159287 | 1.00 (referent) |
| Yes | 9 | 154700 | 1.00 (0.50 to 1.97) |
| Diabetes |  |  |  |
| No | 109 | 2086968 | 1.00 (referent) |
| Yes | 12 | 227020 | 0.88 (0.48 to 1.61) |
| Heart disease |  |  |  |
| No | 96 | 1917789 | 1.00 (referent) |
| Yes | 25 | 396199 | 1.12 (0.72 to 1.75) |
| Bone fracture after age 45 y |  |  |  |
| No | 108 | 2200376 | 1.00 (referent) |
| Yes | 13 | 113612 | 2.20 (1.24 to 3.91) |
| Polyps of the colon or rectum |  |  |  |
| No | 111 | 2035852 | 1.00 (referent) |
| Yes | 10 | 278136 | 0.62 (0.32 to 1.19) |

* $\mathrm{RR}=$ relative risk; $\mathrm{Cl}=$ confidence interval.
$\dagger$ Mean durations of follow-up (and ranges) were 1292 days (87.6-2778 days) for those who developed breast cancer and 2599 days (1-2986 days) for those who did not.
$\ddagger$ RRs were adjusted for age (continuous), ethnicity/race (white vs nonwhite), years of education, and body mass index (per categories shown in Table 2).
male breast cancer through alterations in the bioavailable ratio of estrogen to testosterone $(33,35)$ and would be consistent with the link between breast cancer and Klinefelter syndrome, a condition also associated with low bone density (36).

In terms of lifestyle factors, we found that body mass index was statistically significantly associated with male breast cancer (for $\geq 30$ vs $<25 \mathrm{~kg} / \mathrm{m}^{2}, \mathrm{RR}=1.79,95 \% \mathrm{CI}=$ 1.10 to 2.91) (Table 2), in agreement with case-control studies (11-13,37). Male obesity is often associated with gynecomastia, which has previously been linked with male breast cancer $(29,38)$. However, we did not collect information on gynecomastia.

Obesity is associated with an increased risk of postmenopausal female breast cancer (39), presumably through peripheral conversion of androgens to estrogens (40). In men, obesity is associated with decreased testosterone (41-43) and sex hormone-binding globulin $(41,43)$ levels but increased estrogen levels ( $33,44,45$ ), leading to greater estrogen bioavailability.

As with female breast cancers (46), we found a relationship of risk with physical inactivity that persisted after adjustment for body mass index. Current physical activity was unrelated to the risk of male breast cancer, but physical activity during adolescence was inversely associated with

Table 2. Associations of male breast cancer with body mass index, physical activity, cigarette smoking, and alcohol consumption: National Institutes of Health-AARP Diet and Health Study*

|  | No. of patients $(\mathrm{n}=121)$ | No. of person-years | RRt (95\% CI) | $P$ for trend $\ddagger$ |
| :---: | :---: | :---: | :---: | :---: |
| Current body mass index, $\mathrm{kg} / \mathrm{m}^{2}$ |  |  |  |  |
| <25 | 30 | 667975 | 1.00 (referent) |  |
| $25-<30$ | 53 | 1122408 | 1.07 (0.68 to 1.67) |  |
| $\geq 30$ | 37 | 480509 | 1.79 (1.10 to 2.91) | . 02 |
| Unknown | 1 | 43096 | 0.43 (0.06 to 3.14) |  |
| Frequency of current physical activity |  |  |  |  |
| Never or rarely | 22 | 340273 | 1.00 (referent) |  |
| 1-3 times per month | 10 | 299644 | 0.55 (0.26 to 1.16) |  |
| 1-2 times per week | 25 | 505969 | 0.82 (0.46 to 1.46) |  |
| 3-4 times per week | 31 | 650631 | 0.79 (0.46 to 1.38) |  |
| $\geq 5$ times per week | 27 | 495244 | 0.91 (0.52 to 1.62) | . 91 |
| Unknown | 6 | 22227 | 2.18 (0.71 to 6.67) |  |
| Physical activity between ages 15 and 18 years |  |  |  |  |
| Never or rarely | 11 | 149447 | 1.00 (referent) |  |
| 1-3 times per month | 8 | 121968 | 0.91 (0.37 to 2.26) |  |
| 1-2 times per week | 16 | 304593 | 0.72 (0.33 to 1.55) |  |
| 3-4 times per week | 29 | 569350 | 0.68 (0.34 to 1.37) |  |
| $\geq 5$ times per week | 51 | 1149713 | 0.59 (0.31 to 1.13) | . 07 |
| Unknown | 6 | 18917 | 2.16 (0.65 to 7.18) |  |
| Current physical activity routine |  |  |  |  |
| All day sitting or mostly sitting | 56 | 907672 | 1.00 (referent) |  |
| Walking around a lot but no lifting | 40 | 868592 | 0.69 (0.46 to 1.05) |  |
| Lifting light-heavy loads, heavy work, or climbing stairs or hills | 16 | 493277 | 0.49 (0.28 to 0.87) | . 01 |
| Unknown | 9 | 44447 | 1.96 (0.87-4.41) |  |
| Current smoking status |  |  |  |  |
| Never | 27 | 678464 | 1.00 (referent) |  |
| Former | 72 | 1313008 | 1.26 (0.80 to 1.96) |  |
| Current | 15 | 231537 | 1.67 (0.88 to 3.16) |  |
| Unknown | 7 | 90979 | 1.43 (0.61 to 3.37) |  |
| No. of cigarettes per day |  |  |  |  |
| Never | 27 | 678464 | 1.00 (referent) |  |
| 1-10 cigarettes per day | 15 | 309892 | 1.19 (0.63 to 2.24) |  |
| 11-20 cigarettes per day | 21 | 491106 | 1.01 (0.57 to 1.79) |  |
| 21-30 cigarettes per day | 28 | 333583 | 1.96 (1.15 to 3.33) |  |
| $\geq 31$ cigarettes per day | 23 | 409965 | 1.24 (0.71 to 2.18) | 14 |
| Unknown | 7 | 90979 | 1.43 (0.60 to 3.36) |  |
| Smoking status and duration of cigarette smoking |  |  |  |  |
| Never | 27 | 678464 | 1.00 (referent) |  |
| Former, $\leq 20$ cigarettes per day | 31 | 667816 | 1.10 (0.65 to 1.84) |  |
| Former, $>20$ cigarettes per day | 41 | 645192 | 1.42 (0.87 to 2.32) |  |
| Current, $\leq 20$ cigarettes per day | 5 | 133182 | 0.97 (0.37 to 2.52) |  |
| Current, >20 cigarettes per day | 10 | 98356 | 2.62 (1.26 to 5.47) |  |
| Unknown | 7 | 90979 | 1.43 (0.61 to 3.36) |  |
| Ever smoked pipes or cigars |  |  |  |  |
| Never | 89 | 1596069 | 1.00 (referent) |  |
| Pipes and cigars | 9 | 290106 | 0.51 (0.26 to 1.01) |  |
| Pipes only | 10 | 234901 | 0.75 (0.39 to 1.45) |  |
| Cigars only | 8 | 140707 | 0.92 (0.45 to 1.90) |  |
| Unknown | 5 | 52204 | 1.32 (0.53 to 3.34) |  |
| Alcoholic drink consumption (any kind)§ |  |  |  |  |
| Never | 27 | 479038 | 1.00 (referent) |  |
| <1 drink per day | 59 | 1144516 | 0.99 (0.62 to 1.56) |  |
| 1-3 drinks per day | 19 | 435099 | 0.86 (0.47 to 1.55) |  |
| $\geq 3$ drinks per day | 16 | 255334 | 1.21 (0.65 to 2.25) | . 79 |

* $\mathrm{RR}=$ relative risk; $\mathrm{Cl}=$ confidence interval.
$\dagger$ RRs were adjusted for age, ethnicity/race, years of education, and BMI (as appropriate). BMI was also adjusted for physical activity at ages $15-18$.
$\ddagger$ Tests for linear trends across the exposure categories were calculated by treating these categorical variables as ordinal variables. All statistical tests were two-sided.
§ Separate examination of number of drinks per day of beer, wine, or liquor also showed no relationships with risk.
risk (for activity $\geq 5$ times per week, $R R=$ $0.59,95 \% \mathrm{CI}=0.31$ to 1.13 ). This finding may reflect the importance of sustained physical activity, although imprecise exposure assessment or small numbers must also be considered. Subjects who had a physically active routine were at a statistically significant low risk of male breast cancer ( $\mathrm{RR}=0.49,95 \% \mathrm{CI}=0.28$ to 0.87 ).

Several $(7,15,47)$, although not all $(6,12,13,23,48,49)$, studies have suggested that excessive consumption of alcohol may increase male breast cancer risk. We found no evidence for such a relationship, even when we considered specific types of beverages. However, few individuals reported drinking three drinks per day or more, preventing assessment of previous reports of excess risks among alcoholics $(7,47)$.

Cigarette smokers in our study were at somewhat elevated risk, but there were no convincing trends with intensity or duration of smoking. A statistically significant elevated risk of male breast cancer among current smokers of more than 20 cigarettes per day could have arisen by chance. The absence of a strong effect of smoking is consistent with previous investigations of male $(6,48,49)$, as well as female (50), breast cancer.

Despite its strengths as a prospective investigation, our study had several limitations. Like most previous case-control investigations, our study had relatively few events, limiting our power to detect effects. For more common exposures, such as obesity and physical activity, we had adequate (80\%) power to detect relative risks, but for the less common exposures we had much more limited power (roughly $60 \%$ ), underscoring the need to examine risk factors across multiple studies in pooled analyses. Further, the extent to which our results are generalizable to all male breast cancers is uncertain because the findings were based on self-reported exposures from questionnaires with limited response rates. We were also unable to evaluate all of the proposed hypotheses for male breast cancer, including having late puberty (14); being single, infertile, or childless ( $6,12,14,22,37$ ); having undescended testes; suffering testicular trauma or infections causing orchitis $(14,48)$; and being employed in occupations involving exposure to high temperatures $(22,48,51-54)$ or polycyclic aromatic hydrocarbons $(22,55)$. However, presumably most of these factors would have a limited impact on risk.

Our findings of increased risk associated with obesity and physical inactivity raise concerns about future male breast cancer trends, particularly given recent reports of increasing incidence $(56,57)$. It is unclear, however, whether these reports foreshadow future changes or reflect earlier detection (58). A need for further surveillance, as well as a focus on the role of endogenous hormones that may be associated with these factors, appears warranted. Further, an increased risk of male breast cancer among men with bone fractures indicates that research on androgens and their ratio to bioavailable estrogens may be useful in elucidating mechanisms involved in male breast carcinogenesis.

## References

1. Jemal A, Siegel R, Ward E, et al. Cancer Statistics, 2008. CA Cancer 7 Clin. 2008;58(2): 71-96.
2. Anderson WF, Althuis MD, Brinton LA, Devesa SS. Is male breast cancer similar or different than female breast cancer? Breast Cancer Res Treat. 2004;83(1):77-86.
3. Goodman MT, Tung KH, Wilkens LR. Comparative epidemiology of breast cancer among men and women in the US, 1996 to 2000. Cancer Causes Control. 2006;17(2): 127-136.
4. Ron E, Ikeda T, Preston DL, Tokuoka S. Male breast cancer incidence among atomic bomb survivors. 7 Natl Cancer Inst. 2005;97(8): 603-605.
5. Thomas DB, Rosenblatt K, Jimenez LM, et al. Ionizing radiation and breast cancer in men (United States). Cancer Causes Control. 1994; 5(1):9-14.
6. Casagrande JT, Hanisch R, Pike MC, Ross RK, Brown JB, Henderson BE. A case-control study of male breast cancer. Cancer Res. 1988; 48(5):1326-1330.
7. Olsson H, Ranstam J. Head trauma and exposure to prolactin-elevating drugs as risk factors for male breast cancer. 7 Natl Cancer Inst. 1988;80(9):679-683.
8. Demers PA, Thomas DB, Rosenblatt KA, et al. Occupational exposure to electromagnetic fields and breast cancer in men. Am 7 Epidemiol. 1991;134(4):340-347.
9. Tynes T, Andersen A, Langmark F. Incidence of cancer in Norwegian workers potentially exposed to electromagnetic fields. Am 7 Epidemiol. 1992;136(1):81-88.
10. Erren TC. A meta-analysis of epidemiologic studies of electric and magnetic fields and breast cancer in women and men. Bioelectromagnetics. 2001;(suppl 5):S105-S119.
11. Ewertz M, Holmberg L, Tretli S, Pedersen BV, Kristensen A. Risk factors for male breast cancer-a case-control study from Scandinavia. Acta Oncol. 2001;40(4):467-471.
12. Hsing AW, McLaughlin JK, Cocco P, Co Chien HT, Fraumeni JF Jr. Risk factors for
male breast cancer (United States). Cancer Causes Control. 1998;9(3):269-275.
13. Johnson KC, Pan S, Mao Y. Risk factors for male breast cancer in Canada, 1994-1998. Eur F Cancer Prev. 2002;11(3):253-263.
14. Thomas DB, Jimenez LM, McTiernan A, et al. Breast cancer in men: risk factors with hormonal implications. Am 7 Epidemiol. 1992; 135(7):734-748.
15. Guenel P, Cyr D, Sabroe S, et al. Alcohol drinking may increase risk of breast cancer in men: a European population-based casecontrol study. Cancer Causes Control. 2004;15(6): 571-580.
16. Medras M, Filus A, Jozkow P, Winowski J, Sicinska-Werner T. Breast cancer and longterm hormonal treatment of male hypogonadism. Breast Cancer Res Treat. 2006;96(3): 263-265.
17. Thomas SR, Evans PJ, Holland PA, Biswas M. Invasive breast cancer after initiation of testosterone replacement therapy in a man-a warning to endocrinologists. Endocr Pract. 2008; 14(2):201-203.
18. Kanhai RC, Hage JJ, van Diest PJ, Bloemena E, Mulder JW. Short-term and long-term histologic effects of castration and estrogen treatment on breast tissue of 14 male-to-female transsexuals in comparison with two chemically castrated men. Am 7 Surg Pathol. 2000;24(1):74-80.
19. Symmers WS. Carcinoma of breast in transsexual individuals after surgical and hormonal interference with the primary and secondary sex characteristics. Br Med 7. 1968;2(5597): 83-85.
20. Schatzkin A, Subar AF, Thompson FE, et al. Design and serendipity in establishing a large cohort with wide dietary intake distributions: the National Institutes of Health-American Association of Retired Persons Diet and Health Study. Am 7 Epidemiol. 2001;154(12): 1119-1125.
21. Hill A, Yagmur Y, Tran KN, Bolton JS, Robson M, Borgen PI. Localized male breast carcinoma and family history. An analysis of 142 patients. Cancer. 1999;86(5):821-825.
22. Lenfant-Pejovic MH, Mlika-Cabanne N, Bouchardy C, Auquier A. Risk factors for male breast cancer: a Franco-Swiss case-control study. Int 7 Cancer. 1990;45(4):661-665.
23. Rosenblatt KA, Thomas DB, McTiernan A, et al. Breast cancer in men: aspects of familial aggregation. 7 Natl Cancer Inst. 1991;83(12): 849-854.
24. Palli D, Falchetti M, Masala G, et al. Association between the BRCA2 N372H variant and male breast cancer risk: a populationbased case-control study in Tuscany, Central Italy. BMC Cancer. 2007;7(September 3):170.
25. Tai YC, Domchek S, Parmigiani G, Chen S. Breast cancer risk among male BRCA1 and BRCA2 mutation carriers. 7 Natl Cancer Inst. 2007;99(23):1811-1814.
26. Hultborn R, Hanson C, Kopf I, Verbiene I, Warnhammar E, Weimarck A. Prevalence of Klinefelter's syndrome in male breast cancer patients. Anticancer Res. 1997;17(6D): 4293-4297.
27. Swerdlow AJ, Schoemaker MJ, Higgins CD, Wright AF, Jacobs PA. Cancer incidence and mortality in men with Klinefelter syndrome: a cohort study. 7 Natl Cancer Inst. 2005;97(16): 1204-1210.
28. Evans DB, Crichlow RW. Carcinoma of the male breast and Klinefelter's syndrome: is there an association? CA Cancer $\mathcal{F}$ Clin. 1987;37(4):246-251.
29. Weiss JR, Moysich KB, Swede H. Epidemiology of male breast cancer. Cancer Epidemiol Biomarkers Prev. 2005;14(1):20-26.
30. Sorensen HT, Friis S, Olsen JH, et al. Risk of breast cancer in men with liver cirrhosis. $\operatorname{Am~} \mathcal{F}$ Gastroenterol. 1998;93(2):231-233.
31. Newcomb PA, Trentham-Dietz A, Egan KM, et al. Fracture history and risk of breast and endometrial cancer. Am $\mathcal{F}$ Epidemiol. 2001; 153(11):1071-1078.
32. Ebeling PR. Osteoporosis in men. New insights into aetiology, pathogenesis, prevention and management. Drugs Aging. 1998; 13(6):421-434.
33. Greendale GA, Edelstein S, Barrett-Connor E. Endogenous sex steroids and bone mineral density in older women and men: the Rancho Bernardo Study. 7 Bone Miner Res. 1997; 12(11):1833-1843.
34. Orwoll E, Lambert LC, Marshall LM, et al. Endogenous testosterone levels, physical performance, and fall risk in older men. Arch Intern Med. 2006;166(19):2124-2131.
35. Riggs BL, Khosla S, Melton LJ III. A unitary model for involutional osteoporosis: estrogen deficiency causes both type I and type II osteoporosis in postmenopausal women and contributes to bone loss in aging men. $\mathcal{F}$ Bone Miner Res. 1998;13(5):763-773.
36. Seo JT, Lee JS, Oh TH, Joo KJ. The clinical significance of bone mineral density and testosterone levels in Korean men with nonmosaic Klinefelter's syndrome. B7U Int. 2007; 99(1):141-146.
37. D'Avanzo B, La VC. Risk factors for male breast cancer. $\operatorname{Br} 7$ Cancer. 1995;71(6): 1359-1362.
38. Krause W. Male breast cancer-an andrological disease: risk factors and diagnosis. Andrologia. 2004;36(6):346-354.
39. Ahn J, Schatzkin A, Lacey JV Jr, et al. Adiposity, adult weight change, and postmenopausal breast cancer risk. Arch Intern Med. 2007;167(19):2091-2102.
40. Siiteri PK. Adipose tissue as a source of hormones. Am 7 Clin Nutr. 1987;45(1 suppl): 277-282.
41. Travis RC, Key TJ, Allen NE, et al. Serum androgens and prostate cancer among 643 cases and 643 controls in the European Prospective Investigation into Cancer and Nutrition. Int 7 Cancer. 2007;121(6): 1331-1338.
42. Vermeulen A, Goemaere S, Kaufman JM. Testosterone, body composition and aging. F Endocrinol Invest. 1999;22(5 suppl): 110-116.
43. Wu AH, Whittemore AS, Kolonel LN, et al. Serum androgens and sex hormone-binding globulins in relation to lifestyle factors in older African-American, white, and Asian men in the United States and Canada. Cancer Epidemiol Biomarkers Prev. 1995;4(7): 735-741.
44. Vermeulen A, Kaufman JM, Goemaere S, van Pottelberg I. Estradiol in elderly men. Aging Male. 2002;5(2):98-102.
45. Bjornerem A, Straume B, Midtby M, et al. Endogenous sex hormones in relation to age, sex, lifestyle factors, and chronic diseases in a general population: the Tromso Study. 7 Clin Endocrinol Metab. 2004;89(12):6039-6047.
46. Lahmann PH, Friedenreich C, Schuit AJ, et al. Physical activity and breast cancer risk: the European Prospective Investigation into Cancer and Nutrition. Cancer Epidemiol Biomarkers Prev. 2007;16(1):36-42.
47. Keller AZ. Demographic, clinical and survivorship characteristics of males with primary cancer of the breast. Am 7 Epidemiol. 1967;85(2): 183-199.
48. Mabuchi K, Bross DS, KesslerII. Risk factors for male breast cancer. 7 Natl Cancer Inst. 1985;74(2):371-375.
49. Petridou E, Giokas G, Kuper H, Mucci LA, Trichopoulos D. Endocrine correlates of male breast cancer risk: a case-control study in Athens, Greece. Br 7 Cancer. 2000;83(9): 1234-1237.
50. Lissowska J, Brinton LA, Zatonski W, et al. Tobacco smoking, NAT2 acetylation genotype and breast cancer risk. Int $\mathcal{F}$ Cancer. 2006;119(8):1961-1969.
51. Cocco P, Figgs L, Dosemeci M, Hayes R, Linet MS, Hsing AW. Case-control study of occupational exposures and male breast cancer. Occuр Environ Med. 1998;55(9): 599-604.
52. Ma F, Fleming LE, Lee DJ, et al. Mortality in Florida professional firefighters, 1972 to 1999. Am 7 Ind Med. 2005;47(6):509-517.
53. McLaughlin JK, Malker HS, Blot WJ, Weiner JA, Ericsson JL, Fraumeni JF Jr. Occupational risks for male breast cancer in Sweden. $\operatorname{Br} \mathcal{F}$ Ind Med. 1988;45(4):275-276.
54. Rosenbaum PF, Vena JE, Zielezny MA, Michalek AM. Occupational exposures associated with male breast cancer. Am 7 Epidemiol. 1994;139(1):30-36.
55. Hansen J. Elevated risk for male breast cancer after occupational exposure to gasoline and vehicular combustion products. Am 7 Ind Med. 2000;37(4):349-352.
56. Giordano SH, Cohen DS, Buzdar AU, Perkins G, Hortobagyi GN. Breast carcinoma in men: a population-based study. Cancer. 2004;101(1): 51-57.
57. Hodgson NC, Button JH, Franceschi D, Moffat FL, Livingstone AS. Male breast cancer: is the incidence increasing? Ann Surg Oncol. 2004;11(8):751-755.
58. Anderson WF, Devesa SS. Breast carcinoma in men. Cancer. 2005;103(2):432-433.

## Funding

This research was supported in part by the Intramural Research Program of the National Institutes of Health, National Cancer Institute. The authors had responsibility for the design of the study, collection of data, analysis and interpretation of data, decision to submit the manuscript for publication, and writing of the manuscript.

## Note

Manuscript received March 11, 2008; revised July 31, 2008; accepted August 14, 2008.


[^0]:    Affiliations of authors: Hormonal and Reproductive Epidemiology Branch (LAB, DAR, GLG, JVL) and Nutritional Epidemiology Branch (YP, AS), Knowledge Management, AARP, Washington, DC (ARH).
    Correspondence to: Louise A. Brinton, PhD, Hormonal and Reproductive Epidemiology Branch Division of Cancer Epidemiology and Genetics, National Cancer Institute. 6120 Executive Blvd Suite 550, Rm 5018, Rockville, MD 20852-7234 (e-mail: brinton@ nih.gov).

    See "Funding" and "Note" following "References." DOI: 10.1093/jnci/djn329

    Published by Oxford University Press 2008.

