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THE AUTHORS REPLY: Brugts raises concerns about the use of a polypill for the primary prevention of cardiovascular disease, given pharmacogenetic differences and variability in clinical response among individual recipients. We acknowledge that a variety of factors, including genotype, may affect response to blood-pressure and cholesterol-modifying medications. That said, genetic data are not currently used to guide the implementation of such therapies, given separately or in combination.

The results from our randomized trial add to the accumulating evidence on the effectiveness of polypill-based strategies in persons at risk for cardiovascular disease.[1-3] Such an approach may be particularly useful in contexts in which frequent clinic visits, repeated laboratory testing, and genotyping are not easily accessible. Further trials may be warranted to compare highly tailored approaches, as advocated by Brugts, with simpler strategies.

Bilal and Cainzos-Achirica raise the importance of addressing underlying social and economic drivers of disease in vulnerable populations — a recognition that is also emphasized in the recent national practice guideline for the primary prevention of cardiovascular disease.[4] We agree with the need to better understand and address fundamental root causes of disparities in cardiovascular health. The polypill represents just one of several potential tactics that may be useful in reducing the inequalities in cardiovascular outcomes. A pharmacologic strategy such as the polypill should not preclude the pursuit of lifestyle interventions and policies to address the social and medical vulnerabilities of low-income persons.

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Since publication of their article, the authors report no further potential conflict of interest.

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Epidemiologic Signatures in Cancer

TO THE EDITOR: Welch et al. (Oct. 3 issue)[1] report trends in cancer incidence and mortality that suggest overdiagnosis, but differential trends in the incidence of ductal carcinoma in situ (DCIS) and invasive breast cancer are also informative. The long-held assumption that DCIS is a precursor to invasive breast cancer was based on two observations: DCIS is often found adjacent to invasive tumor foci, and after simple excision of DCIS, recurrences occur — and these recurrences are frequently invasive breast cancer.[2] In the United States, the increased use of mammography screening between the years 1975 and 2004 led to a dramatic increase in the age-adjusted incidence of DCIS (from 5.8 to 32.5 cases per 100,000 women), and extirpation of these lesions should have produced a substantial decline in the incidence of invasive breast cancer. Nonetheless, the age-adjusted incidence of invasive breast cancer climbed from approximately 100.0 to 124.3 cases per 100,000 women during the same period.[3] This raises doubts about ingrained assumptions

concerning the natural history of DCIS and suggests that mammography is tapping into a large reservoir of occult, nonprogressive DCIS.[4]

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: The epidemiologic signatures in cancer that were devised by Welch and colleagues did not, as presented, reflect considerations of age effects. When analyzed for age effects,[1,2] the trends in the incidence of prostate cancer and breast cancer are distinctly different.

As can be expected as a consequence of the detection of slow-growing cancers, decades of prostate-specific antigen (PSA) screening decreased the incidence of prostate cancer among men over 75 years of age. Nearly four decades of screening mammography in the United States has not, however, decreased the incidence of breast cancer among women 75 years of age or older (Fig. 1), despite a majority of breast cancers in younger women being detected. We have observed this difference in every country that has been conducting prostate and breast screening since the 1980s, along with an excess of breast cancer incidence among elderly persons, accompanied by excess mortality.

Radiation is used for screening for breast cancer, whereas nonradiation methods are used for prostate and cervical cancer. This comparison gives support to the possibility that mammograms have caused a high incidence of cancers[3] among older women.

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THE AUTHORS REPLY: Jatoi and Benson summarize the failure of the increasing detection and treatment of DCIS in reducing the occurrence of invasive breast cancer. We agree that there is only weak evidence that DCIS is a precursor — much less an obligate precursor — of invasive breast cancer. Nevertheless, the treatment of DCIS is often as aggressive as that of stage I invasive cancer (in both groups, approximately a third of patients undergo mastectomy, according to the SEER data). Consequently, DCIS is an important component of overdiagnosis and overtreatment attributable to mammography.

Corcos and Bleyer highlight the distinct effects of breast and prostate cancer screening on cancer incidence in the elderly population. Although we share the concern about radiation-induced cancers caused by diagnostic imaging (a concern that extends well beyond mammography), we suspect that the distinct incidence trends in elderly persons primarily reflect distinct practice patterns — not radiation.

Screening mammography utilization in the United States has been relatively stable over time[1]; thus, the persistent increase in incidence probably reflects continued screening in this age group (and the absence of an expected compensatory decline suggests overdiagnosis). PSA screening, however, has declined over time.[2] Furthermore,

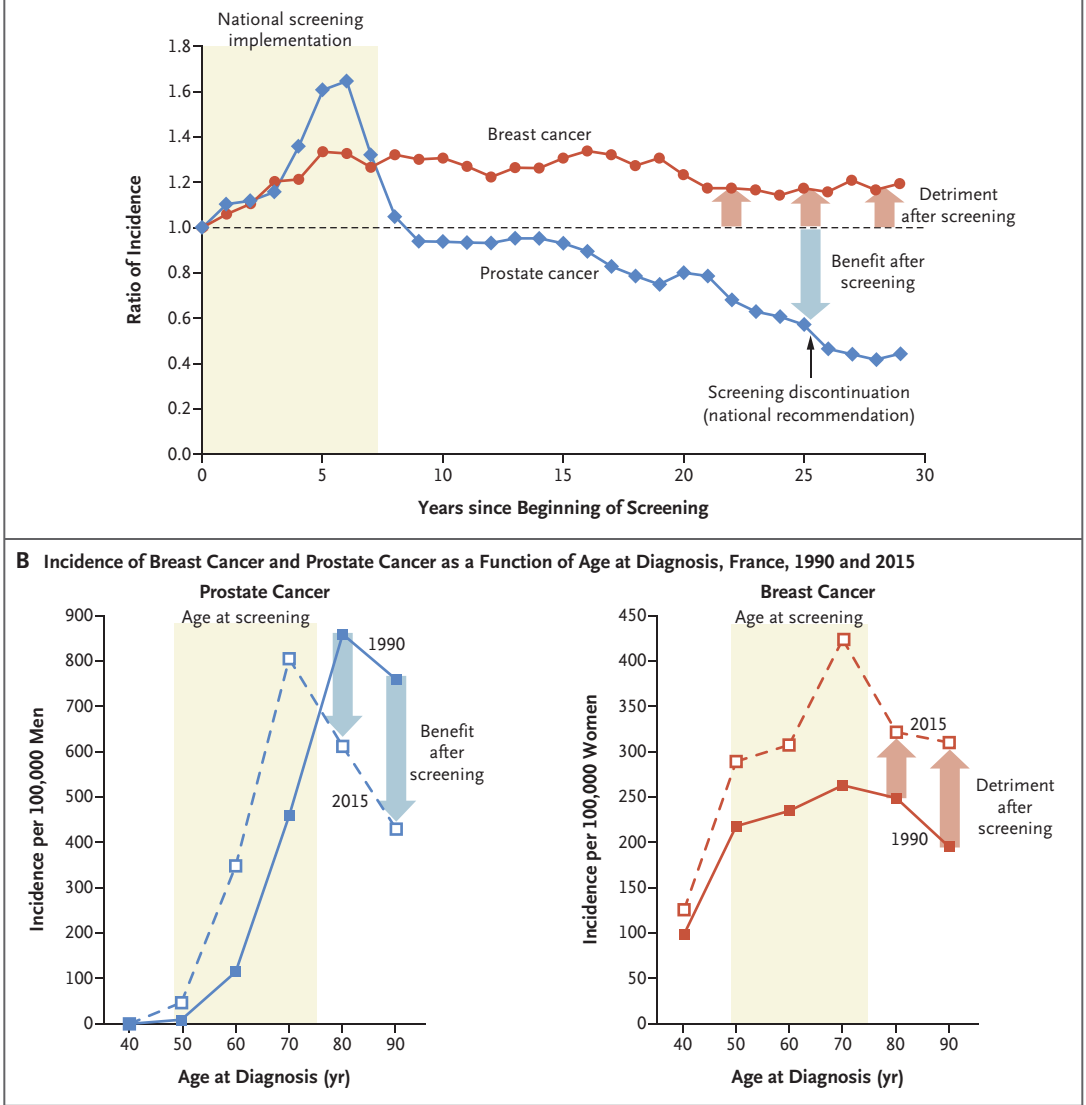

Figure 1. Changes in Prostate and Breast Cancer Incidence after Screening Implementation in the United States and France.

Data for the United States are from the Surveillance, Epidemiology, and End Results (SEER) Program and are based on the annual incidence of prostate and breast cancer among persons older than 75 years of age (1975 through 2016; SEER 9 regions); analyses were performed with the use of SEER*Stat (age-adjusted rates). Data for France are the annual cancer incidence as a function of age before (1990) and after (2015) widespread prostate-specific antigen and mammography screening and are from Public Health France.

as early as the year 2000, even the American Urological Association argued that screening should not be performed in men with a life expectancy of less than 10 years.[3] Our best guess is that the importance of not screening patients with a limited life expectancy is more broadly recognized in prostate cancer than in breast cancer. In particular, urologists may routinely use higher PSA thresholds for prostate biopsy in elderly men.

The fact that we have to guess, however, speaks volumes about the need for better data

on population-based screening. In our article, we argued for the collection of data on the mode of cancer detection (i.e., clinically detected, detected by screening, or incidentally detected). Equally important, however, is routine collection of data on the frequency of screening in various age groups, as well as the thresholds used in practice to pursue biopsy.

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Reporting Adverse Events for Cannabis to the FDA

TO THE EDITOR: We would like to clarify a statement in the letter by Mudan et al. (Sept. 12 issue)[1] suggesting the lack of a national pharmacovigilance database for reporting adverse events associated with products containing cannabis. Consumers and health care professionals can directly report to the FDA MedWatch program[2] adverse events and other problems, such as product quality issues or medication errors, that they believe are associated with medical products. Although the majority of reports received are for FDA-approved products, reports regarding unapproved products, including cannabis and cannabis-derived products, are accepted through this pathway. The FDA has received reports of adverse events in patients using cannabis or cannabis-derived products to treat medical conditions and recreationally. The FDA conducts routine surveillance of all adverse-event reports for safety signals, including those involving cannabis use, with a focus on serious adverse effects. Information about the regulation of cannabis and cannabis-derived products by the FDA is provided at www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-questions-and-answers. Health care professionals and consumers are encouraged to report adverse events and other problems related to the use of these products to the FDA MedWatch program.[2]

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The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Food and Drug Administration.

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