



Women's Reproductive Cancers in Evolutionary Context

Author(s): S. Boyd Eaton, Malcolm C. Pike, Roger V. Short, Nancy C. Lee, James Trussell, Robert A. Hatcher, James W. Wood, Carol M. Worthman, Nicholas G. Blurton Jones, Melvin J. Konner, Kim R. Hill, Robert Bailey, A. Magdalena Hurtado

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WOMEN'S REPRODUCTIVE CANCERS
IN EVOLUTIONARY CONTEXT

S. BOYD EATON

*Department of Radiology
Emory University School of Medicine
Atlanta, Georgia 30322 USA*

MALCOLM C. PIKE

*Department of Preventive Medicine
University of Southern California
School of Medicine
Los Angeles, California 90033-9987 USA*

ROGER V. SHORT

*Department of Physiology
Monash University
Clayton, Melbourne, Victoria, 3168 Australia*

NANCY C. LEE

*Cancer Prevention and Control Branch
Centers for Disease Control and Prevention
Atlanta, Georgia 30030 USA*

JAMES TRUSSELL

*Office of Population Research
Princeton University
Princeton, New Jersey 08544-2091 USA*

ROBERT A. HATCHER

*Department of Gynecology and Obstetrics
Emory University School of Medicine
Atlanta, Georgia 30303 USA*

JAMES W. WOOD

*Department of Anthropology and
Population Issues Research Center
Pennsylvania State University
University Park, Pennsylvania 16802 USA*

CAROL M. WORTHMAN

*Department of Anthropology
Emory University
Atlanta, Georgia 30322 USA*

NICHOLAS G. BLURTON JONES

*Departments of Education,
Anthropology and Psychiatry
University of California at Los Angeles
Los Angeles, California 90024 USA*

MELVIN J. KONNER

*Department of Anthropology
Emory University
Atlanta, Georgia 30322 USA*

KIM R. HILL

*Department of Anthropology
University of New Mexico
Albuquerque, New Mexico 87131 USA*

ROBERT BAILEY

*Department of Anthropology
University of California at Los Angeles
Los Angeles, California 90024 USA*

A. MAGDALENA HURTADO

*Department of Anthropology
University of New Mexico
Albuquerque, New Mexico 87131 USA*

In citing this article, the authors should be listed in the following order: Eaton, Pike, Short, Lee, Trussell, Hatcher, Wood, etc.

Reprint requests should be addressed to Dr. S. Boyd Eaton, Department of Radiology, West Paces Ferry Hospital, 3200 Howell Mill Road, N.W., Atlanta, Georgia 30327 USA.

ABSTRACT

Reproductive experiences for women in today's affluent Western nations differ from those of women in hunting and gathering societies, who continue the ancestral human pattern. These differences parallel commonly accepted reproductive risk factors for cancers of the breast, endometrium and ovary. Nutritional practices, exercise requirements, and body composition are nonreproductive influences that have been proposed as additional factors affecting the incidence of women's cancers. In each case, these would further increase risk for women in industrialized countries relative to forager women.

Lifestyles and reproductive patterns new from an evolutionary perspective may promote women's cancers. Calculations based on a theoretical model suggest that, to age 60, modern Western women have a breast cancer risk as much as 100 times that of preagricultural women.

THE HEALTH STATUS of any population may be considered to reflect an interaction between inherent genetic makeup and lifestyle factors that affect disease initiation and progression. The genetic component of this relationship is relatively constant over time in contrast to operative lifestyle influences that can change profoundly over just a few decades. While natural selection has made small changes in the human gene pool during the past 10,000 years, from a genetic standpoint we remain nearly identical to our remote ancestors of that time (G. C. Williams and R. M. Nesse, in press). Allelic frequencies have been altered by migration and differential population expansion, but such changes are unlikely to have systematically affected human susceptibility to today's most prevalent chronic illnesses because (1) the latter generally produce mortality after child rearing has been completed and (2) the susceptibilities of Africans, Asians, and Europeans to a given chronic illness are essentially (though not absolutely) similar. [The pattern for infectious diseases differs because these conditions commonly kill in childhood and hence exert greater selection pressure (and hence more rapid change in allelic frequencies), and also because multiple gene populations, human and microbial, must coevolve with one another, as well as be affected by environmental factors such as urbanization, sanitation, immunization, and antibiotic therapies.]

These considerations suggest that the lifestyle for which current human genetic makeup has been selected is actually that of Stone Age foragers, and that recent lifestyle modifications have altered our basal or "naturally" expected health status.

For many illnesses, particularly those influenced by multiple genetic loci, a population's

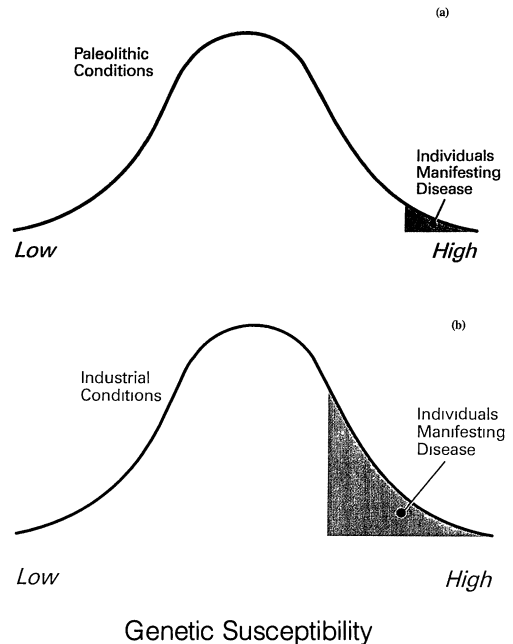


FIG. 1. GENES, LIFESTYLE, AND CHRONIC DEGENERATIVE DISEASE

The genetic susceptibility of current humans, for any given chronic degenerative disease, is similar to that of our preagricultural, but anatomically modern, ancestors. The interaction between current lifestyle factors and ancient genetically determined biology, however, produces far greater disease expression in today's affluent nations.

genetically determined susceptibility may approach a normal distribution. This article proposes that present-day lifestyle factors have markedly elevated the incidence of women's cancers relative to their retrodicted rates among our preagricultural ancestors (Fig. 1).

Nutrition, physical activity, and social customs in today's industrial nations differ from

those of recently studied foragers. Here we present evidence that reproductive experiences of women in affluent countries also differ from those of women still living in preagricultural settings much like those that existed before the Neolithic Revolution of 10,000 years ago. The reproductive patterns of women in hunting and gathering economies share many features with those of nonhuman anthropoid primates; these common elements may contribute to a genetically programmed model for higher primates generally. Compared with this evolutionary paradigm, women in today's industrial states experience earlier menarche, lower parity, and probably later menopause. Lactation, if any, is of much reduced frequency and duration. Conversely, ovulation and menstruation occur much more often; during their lives American women experience approximately three times as many menstrual periods as women who have continued the lifeways of our early ancestors.

The evidence that women's cancers are related to reproductive biology has become convincing; the evidence concerning relationships between nonreproductive lifestyle factors and the same malignancies is controversial, but suggestive. In addition, increasing pathophysiological data indicate how influences of both types might affect tumorigenesis. It is not the purpose of this article to critically evaluate available epidemiological evidence, nor to rank the importance of individual risk factors. Rather, its aim is to show that the best established risk factors represent deviations from hunter-gatherer (and, by extension, ancestral human) experience. Further, we attempt to integrate epidemiological and anthropological studies to allow comparison of reproductive cancer risk for women in industrial nations with the theoretical risk for women who experienced life in preagricultural circumstances.

COMPARATIVE REPRODUCTIVE CONSIDERATIONS

Nonhuman Primates

The reproductive experiences of free-living gorillas and chimpanzees are roughly equivalent. These animals are our closest living relatives, although a common ancestor probably existed no more recently than five to seven million years ago. Despite this long evolution-

ary separation, DNA hybridization studies suggest that the three species now differ genetically by less than 2% (Sibley, 1987). Given such similarity, it is intriguing to note that reproductive cancers now common in women are rarely encountered in nonhuman primates: One ovarian adenocarcinoma, no endometrial cancers, and no breast cancers in 1065 nonhuman primate necropsies (Seibold and Wolf, 1973).

For free-living chimpanzees menarche occurs between ages 10 and 11.5, with first birth typically about two years thereafter. Duration of lactation per birth (3.5–4 years), nursing frequency (for gorillas twice hourly in daytime with additional nursing at night), and completed family size (5) are much like comparable data for preagricultural forager women (Tutin and McGinnis, 1981; Goodall, 1986; Stewart et al., 1988; Galdikas and Wood, 1990).

Hunter-Gatherers

Women living in foraging societies have afforded our best opportunity to observe the "natural" pattern of human female reproduction, free from the changes introduced by scientific, technological, and cultural innovations during the past few centuries.

Menarche in hunter-gatherers occurs at about age 16 (Table 1), similar to the age in 19th century Western nations (Tanner, 1973) and to that of Japanese (15.3 years) and rural Chinese (17.1) as late as the 1940s (Nagai et al., 1980; Key et al., 1990). Average age at first birth for foragers is about 19.5, so the interval between menarche and first birth is about 3.5 years, little more than that for free-living great apes (1.5–2.5 years), but far different from current American experience (see below).

Infants in preagricultural societies are breast-fed: Traditional !Kung San, like other foragers, nurse for the first three or four years of a child's life. The frequency of nursing is even more surprising than its duration, and parallels that observed among anthropoid primates in the wild. Average !Kung San mothers nurse four times an hour during the day and several additional times at night throughout the child's first two years (Konner and Worthman, 1980). Even though solid foods are generally intro-

TABLE 1
Hunter-Gatherer Reproduction

	!Kung	Aché	Agta	Traditional Eskimos	Australian Aborigines	Hadza	Hiwi	Efe*	Mean
Menarche	16.6	15.3	17.1	15.5	—***	—	—	16.0	16.1
First birth	19.9	19.5	20.1	18.6	18.5	20.0	—	20.0	19.5
Duration of lactation per birth (years)	3.5	2.1	—	3.0	3.5	2.5	—	—	2.9
Completed family size**	4.7	8.0	6.5	6.2	5.0	5.7	5.1	—	5.9

* R. Bailey (pers. commun.)

** Mean number of live births in women who survive to age 50.

*** A dash represents a lack of data.

Sources: Weyer, 1932; Oswalt, 1963; Abbie, 1969; Hamilton, 1979; Milan, 1980; Goodman et al., 1985; Hill and Hurtado, 1987; Campbell and Wood, 1988; Cohen, 1989; Blurton Jones et al., 1992; Hill and Hurtado, in press.

duced at about 6 months, mothers' milk remains the major source of nutrients until the eruption of molar teeth (at 15 to 18 months), and is a significant part of the child's nutrition well into the third year of life.

Nursing this frequent is sufficient to suppress ovulation (R. H. Gray et al., 1990)—24 months for !Kung San and 30 months for traditional Australian Aborigines (Abbie, 1969; Hamilton, 1979; Konner and Worthman, 1980). This practice largely explains the long interval between births (averaging about three years) as well as the relatively low reproductive output (average completed family size of about 5.9 live births in women who survive for the whole of their reproductive span) in forager societies.

Estimating age in older hunter-gatherers is difficult, and since menstrual cycles occur irregularly near the end of a woman's reproductive span, her age at menopause is especially hard to document. The mean age at last birth or at menopause has been estimated for several forager populations, and an endocrine marker (persistently elevated luteinizing hormone concentration) has been used to determine menopausal age for Hadza in Tanzania and Gainj in New Guinea (Phillips et al., 1991; Wood, 1991). Together these data suggest an average age at menopause of about 47 years.

The number of lifetime ovulations can be estimated by subtracting age at menarche (16) from age at menopause (47) and multiplying by 13 ovulations per year, yielding 403 possible ovulations. Since forager women bear an

average of 6 children, 198 months are anovulatory (9 months pregnancy plus 24 months postpartum anovulation for each child); allowing for 13 cycles per 12 months, 215 ovulations are thereby suppressed. Subtracting suppressed from possible yields 188 ovulations. About 30 additional postmenarcheal and premenopausal anovulatory cycles probably occur, leaving perhaps 160 lifetime ovulations for hunter-gatherer women who live beyond menopause. Even after this correction the estimate remains inexact, since miscarriages and stillbirths, as well as infant mortality, are disregarded. The former factors would act to increase suppressed ovulations whereas the latter, by shortening duration of lactation, abbreviates lactational anovulation.

Contemporary Americans

In contemporary America the mean menarcheal age is 12.5 years, a figure consonant with those for other industrialized countries (Marshall and Tanner, 1986). The level of educational attainment is correlated with average age at first birth: over 27 years for women born after 1955 who have earned a college degree, 26.4 years for all women with some education beyond high school, and about 24.0 years for all American women, regardless of education. Later age at first birth and declining menarcheal age have widened the interval between these events (the so-called "nubility spread") to nearly 14 years for moderately educated women. Furthermore, the prevalence of permanent childlessness has increased; cur-

TABLE 2
Reproductive Experience and Risk of Women's Cancers

	Reproductive contrasts		Significance for cancer risk		
	Hunter-gatherers	Americans	Breast	Endometrium	Ovary
Age at menarche	16.1	12.5	+	+	
Age at first birth	19.5	24.0 (all) 26.5 (educated*)	+		
Menarche to first birth time elapsed, years	3.4	11.5 (all) 14.0 (educated*)	+		
Duration of lactation per birth	2.9 years	3.0 months	+		+
Completed family size***	5.9	1.8	+	+	+
Age at menopause	47	50.5	+	+	
Total number of ovulations (see text for calculations)	160	450**			+

* Women with at least some education beyond high school.

** For women who have not used oral contraceptives.

*** Mean number of live births in women who survive to age 50.

rent predictions range from 15 to 25%, compared with the 10% rate observed in the early decades of this century (Bloom, 1986).

During the 1970s breast-feeding experienced a resurgence in the United States, but thereafter its popularity declined. In 1989 only 52% of American infants were ever breast-fed and only 7% were breast-fed for as long as 12 months (Ross Laboratories Mother's Surveys, 1991).

Average age at menopause in the United States is about 50.5 years, a figure similar to those for other industrialized nations (Snowdon et al., 1989). Demographers disagree as to whether age at menopause has increased significantly as a consequence of industrialization: Some contend there was a gradual rise from an undetermined earlier age to the current figure between roughly 1800 and 1950, while others maintain that menopausal age has been relatively constant since the Classical Period. In 1850 the average menopausal age for English and Scottish women was estimated to be about 47.5 years (Frisch, 1978), a value close to that suggested for recent hunter-gatherers.

There is no comparable dispute about trends in average fertility. During this century, the average completed family size of American women has declined from about 3.8 to about 1.8, a value similar to that for other developed nations (UNICEF, 1987; Haines, 1989).

The prevalence of oral contraceptive (OC) use complicates calculation of current average

lifetime ovulations. In 1987, 80% of American women had used OCs at some point in their lives (Dawson, 1990), a factor pertinent to calculation of women's cancer risk (see below). For didactic simplicity, however, the following calculations arbitrarily omit consideration of OC use and estimate lifetime ovulations for Americans as for hunter-gatherers.

Subtracting age at menarche, 12.5, from age at menopause, 50.5, and multiplying by 13 ovulations per year yields 494 possible ovulations. Americans have an average of 1.8 children and breast-feed for a short time, if at all, so they experience only 21.6 anovulatory months (for each child: 9 months pregnancy plus 3 months postpartum anovulation)—about 23 suppressed ovulations. When these are subtracted from the potential maximum, 471 remain. Because of earlier menarche, Americans should experience less peripubertal anovulation than foragers (MacMahon et al., 1982; Apter and Vihko, 1983). Subtracting 20 postmenarcheal and premenopausal cycles yields about 450 total ovulations (Table 2).

Like that generated for hunter-gatherers, this estimate is "rough." It disregards infant mortality, a factor less significant now than previously, but it also ignores surgically induced abortions which, like miscarriages, would increase the number of suppressed ovulations. In any case, the ovulatory discrepancy between hunter-gatherers and current Americans must be large.

REPRODUCTIVE FACTORS AND CANCER

Breast Cancer

Epidemiological studies indicate that late menarche, early first birth, high parity, early menopause, and possibly lactation all reduce the risk of breast cancer (Brinton et al., 1988; Kelsey and Berkowitz, 1988; Layde et al., 1989). The influence of parity is complex: Full-term pregnancies cause a transient initial increase in breast cancer risk followed by a long-lasting protective effect (Bruzzi et al., 1988; E. M. Williams et al., 1990).

The breast's susceptibility to carcinogenesis is directly related to its epithelial cell proliferation rate and inversely related to its degree of tissue differentiation. Thymidine labeling studies show the highest breast epithelial mitotic rates in young women, especially during the first five years after menarche. Microscopic studies of mammary development in rodents have shown that the postpubertal but nonparous breast contains large numbers of undifferentiated terminal end buds (analogous to intralobular terminal ducts in young women). The epithelial cells of these structures appear especially susceptible to carcinogenic agents and are likely sites for neoplastic transformation. Pregnancy and lactation induce differentiation of these elements into well-developed secretory lobules which, in animals, have a slower proliferative rate and more resistance to chemical carcinogenesis (Russo et al., 1987). Accordingly, between puberty and first pregnancy the breast is especially vulnerable to neoplastic initiation.

Autoradiographic studies of human mammary tissue indicate that estrogen accelerates breast epithelial proliferation (Anderson et al., 1989), and numerous investigators believe that increased exposure to estrogen elevates breast cancer risk (Key and Pike, 1988b). The breast cancer rates of women in recently studied hunter-gatherer societies are unknown, but their estrogen levels are low (Van der Walt et al., 1978). Asian women, whose breast cancer incidence rates are less than those of Westerners (Yuan et al., 1988), have significantly lower serum and urinary estrogen levels (Key et al., 1990). Japanese and Chinese Americans have higher estrogen levels and greater breast cancer rates than those found in Japan and China (Buell, 1973; Trichopoulos et al., 1984). The

increased risk of breast cancer in obese postmenopausal women is thought to reflect aromatization of adrenal androgens to estrogens by adipose tissue so that, after menopause, obese women have higher blood levels of estrogen (Kirschner et al., 1982). Furthermore, studies of the relationship between estrogen replacement therapy and breast cancer increasingly suggest a positive association (Steinberg et al., 1991; G. A. Colditz, unpublished data).

Endometrial Cancer

The likelihood of developing endometrial carcinoma is also influenced by reproductive experience. Early menarche, late menopause, and especially low parity are considered to increase risk (LaVecchia et al., 1984; Kvale, Heuch, and Ursin, 1988). Exogenous replacement estrogen elevates risk, but combination oral contraceptives (COCs) confer protection (Cancer and Steroid Hormone Study, 1987).

These observations have led to the formulation of an "estrogen excess hypothesis" (Henderson et al., 1982). Women with endometrial cancer typically exhibit signs of high estrogen effect, including ovarian stromal hyperplasia and a high vaginal cornification index; furthermore, their plasma estrogen levels are higher than those of controls. The association of obesity with endometrial carcinoma supports this hypothesis: Obese postmenopausal women have higher estrogen levels; both premenopausal and postmenopausal obese women have lower concentrations of sex hormone binding globulin (SHBG) and hence a greater proportion of bioavailable estrogen; obese premenopausal women exhibit relative progesterone deficiency. Progesterone exerts a protective influence because, in the uterus, it opposes the proliferative effect of estrogen and reduces endometrial cell proliferation during the later luteal phase (Key and Pike, 1988a). Progesterone's protective action is especially evident in the beneficial influence of COCs, which contain both estrogen and progesterone, in contrast to the adverse effects of replacement estrogen alone (Henderson et al., 1982).

Ovarian Carcinoma

Like cancers of the breast and endometrium, epithelial ovarian carcinoma is related to reproductive experience: Increasing parity and

OC use are important protective influences (Kvale, Heuch, Nilssen, and Beral, 1988; Villard-Mackintosh et al., 1989; Gwinn et al., 1990). Furthermore, the "incessant" ovulation hypothesis (Fathalla, 1971) proposes that each ovulation mechanically injures the ovarian epithelium, while exposing it to locally high hormonal levels from escaping follicular contents. Pregnancy and oral contraceptives reduce the total number of ovulations as does lactation (for which a protective effect has been shown by some, but not all investigations). Pregnancies and oral contraceptives may have additional protective effects, but decreased ovulatory frequency is probably an important element whereby these factors reduce risk of ovarian malignancy. In any event, the high number of ovulations experienced by women in Western nations represents a departure from an earlier human reproductive pattern, a departure that may strongly influence the incidence of ovarian epithelial carcinoma.

In view of these demonstrated relationships, we can surmise that the reproductive risk factors for women's cancers suggested by epidemiological investigations are largely, though not exclusively, a recapitulation of reproductive differences between women in affluent 20th century nations and women living before the advent of agriculture. The experiences of our ancestors were more representative of the higher primate pattern and hence in better accord with the genetic patterns transmitted to modern women via the long course of hominoid/hominid evolution. Each factor listed in Table 2 would have tended to protect paleolithic women, but tends to increase cancer risk for women in today's world.

EXTRAREPRODUCTIVE FACTORS

Nutrition

Dietary Fat

Reducing fat intake may lower serum estrogen concentrations in both premenopausal and postmenopausal women (Rose et al., 1987; Prentice et al., 1990), while epidemiological surveys (G. E. Gray et al., 1979; Prentice et al., 1988) and investigations in laboratory animals (Carroll, 1980) strongly suggest that increased dietary fat promotes breast tumor

development. Women in the United States, who until recently consumed about 40% of their calories as fat, have roughly 5 times the risk of breast cancer as have women in Japan, where fat makes up only about 19% of total caloric intake (Schatzkin et al., 1989). In rodents, a high-fat diet significantly increases the incidence of mammary tumors at all levels of total caloric intake (Tannenbaum, 1945).

Conversely, several recent cohort and case-control studies have failed to show a relationship between dietary fat intake and the development of breast cancer in the women studied (Howe, 1992). The differing results, however, are not inherently contradictory. The investigations that did not show a relationship between dietary fat and breast cancer involved subjects who were adults at the inception of the study periods, but the effects of diet on women's cancers may be most critical early in life (Eveleth and Tanner, 1990). Furthermore, these studies involved the range of fat intake now prevalent in the United States, whereas the protective effects of a low-fat diet may emerge only at a level below that of nearly all the subjects studied.

Such low levels may be "natural" for our species: Fat intake for late paleolithic humans (i.e., anatomically modern people living between 40,000 and 15,000 years ago), after weaning, probably provided from 20 to 25% of total daily energy (Eaton, 1992; Table 3). It is unlikely that any human ancestral species during the past 40 million years consumed as much as 30% of its total caloric energy as fat. Perhaps the putative benefits of dietary fat reduction, with regard to breast cancer, will become apparent only when intake levels of about 20% of total caloric energy are in effect from childhood on.

Dietary Fiber

Breast cancer incidence and fiber intake have been negatively correlated in several studies, and fiber's possible antineoplastic effect might result from one or more of several potential mechanisms (Hughes, 1990). Estrogens are deactivated in the liver and excreted via the bile. A high-fiber diet decreases intestinal reabsorption of estrogenic hormones (Hughes, 1990). Moreover, fiber-rich diets provide mammalian lignins. These weakly estrogenic substances stimulate hepatic synthesis of SHBG, thus reducing plasma free-estrogen levels; they may

TABLE 3
Extrareproductive Factors Affecting Risk of Women's Cancers

	Hunter-gatherers	Typical Americans
Dietary fat, % energy	20	36*
Dietary fiber, g/d	100	15
Maximal O ₂ consumption, ml/kg/min**	51.8	42.5
Triceps skinfold, mm	9.6***	17.0

* 36% in 1985-1986; 41% in 1977-1978.

** VO₂ max is a measure of aerobic (endurance) fitness. The values are for young men; women's data are unavailable, but believed comparable.

*** Australian Aborigines, 9.4; Tanzanian Hadza, 9.8.

Sources: Abbie, 1963; Eveleth and Tanner, 1976; Hiernaux and Boedhi Hartono, 1980; Eaton et al., 1988; Committee on Diet and Health, National Research Council, 1989.

inhibit conversion of adrenal steroid precursors to estrogens by adipose tissue; and they may act directly as antiestrogens—competitively inhibiting the action of estrogen at the cellular level (Adlercreutz et al., 1988).

In comparison with controls, breast cancer patients have low levels of mammalian lignins; conversely, nonhuman primates, who appear relatively resistant to the carcinogenic effects of estrogen (Pfeiffer and Allen, 1948; Geschickter and Hartman, 1959), have high levels (Adlercreutz et al., 1986). Like preagricultural humans, for whom fiber intake approaching 100 gms/day has been estimated (Eaton, 1990; Table 3), nonhuman primates consume large amounts of fiber-containing foods, which their high mammalian lignin levels apparently reflect.

Exercise

The habitual physical activity of our preagricultural ancestors exceeded that prevalent in today's Western nations. For example, traditional !Kung women are estimated to walk 2,400 km annually, or about 6.6 km/day, while carrying equipment, gathered material, and a child. On the return leg of a day's foraging trip, a woman will have gathered 7 to 15 kg of plant food, and a typical !Kung mother will carry her child some 7,800 km during its first four years of life (Lee, 1979). Exercise of this magnitude might affect women's reproductive experience both directly and indirectly (Ellison and Lager, 1986; Bernstein et al., 1987).

The influence of exercise on women's cancers may be important. While not all investigators concur (Paffenbarger et al., 1992), one study of 5,000 college alumnae (Frisch et al.,

1985) showed that former varsity athletes were much more likely to have trained extensively in high school and somewhat more likely to have exercised regularly after college than were their classmates. The nonathletes experienced earlier menarche and slightly later first birth, and their rates of breast, uterine and ovarian cancer varied from nearly twice to five times those of the athletes, whose exercise experience more closely resembled that of preagricultural women.

Body Composition

Obesity is the constitutional risk factor most commonly associated with endometrial carcinoma (Kelsey et al., 1982), and it has been found to be an independent risk factor for breast cancer in postmenopausal women, especially those with truncal obesity (Folsom et al., 1990; Sellars et al., 1992), although not in all studies (Petrek et al., 1993). Adipose tissue converts adrenal precursors to estrogens and is inversely related to SHBG levels, so obese women have more bioavailable estrogen than do their normal-weight peers, especially after menopause (Key and Pike, 1988a). Thus the relationship of both endometrial and postmenopausal breast cancer to obesity fits with the estrogen excess hypothesis.

Most preagricultural women were leaner than current Western women: Their lives required more physical exertion and they had limited access to energy-dense foodstuffs. On average, the skinfold thickness of American women is almost twice that of recently studied hunter-gatherers (Eveleth and Tanner, 1976; Hiernaux and Boedhi Hartono, 1980; Eaton et al., 1988).

TABLE 4
Estimated Cumulative Relative Cancer Risk to Age 60 (see Appendix)

	Breast	Epithelial ovarian	Endometrial
Paleolithic hunter-gatherers*	1	1	1
Americans with 10 years COC use	114**	6.9	75
Americans who have not used COCs	114	24	240

* About 9% of hunter-gatherers reach age 60 and beyond (Howell, 1979).

** See Mann (1990) for a discussion of this relationship.

The computations used to derive this table are generated by a modification of Pike's model (Pike et al., 1983; Pike, 1987; see Appendix). The underlying assumptions are detailed in the original papers.

In addition to their putative direct effects, these extrareproductive lifestyle factors may act in concert to influence reproductive experience—especially age at menarche (Frisch et al., 1981; Micozzi, 1985; Merzenich et al., 1993)—and thus indirectly elevate the risk faced by contemporary women (Table 3).

DISCUSSION

The data upon which this article depends have been obtained only with difficulty. The limited information available on reproduction in the great apes has been accumulated only after decades of near continuous observation in the wild, and studies of nomadic foragers have been beset with obstacles only slightly less formidable. Inexact communication, natural reluctance to discuss intimate subjects, and the inherent frailty of human memory have all hindered collection of accurate data. Indeed, considering such problems, the consistency of the findings presented in Table 1 is remarkable.

Possible linkages between reproductive events and women's cancers have also been difficult to establish: The strength and even the existence of such relationships have varied from study to study. And while there is growing consensus about reproductive epidemiology, the nature and importance of nonreproductive risk factors for women's cancers remain highly contentious.

A final, serious problem is the near-total lack of data about women's cancer frequency among recently studied hunter-gatherers, let alone for humans living before the Agricultural Revolution. Medical anthropologists have

found little cancer in their studies of technologically primitive people, and paleopathologists believe that the prevalence of malignancy was low in the remote past, even when differences in population age structure are taken into account (Rowling, 1961; Hildes and Schaefer, 1984; Micozzi, 1991). Still the data are meager at best.

This difficulty may be addressed by employing a modification of the incidence model developed by Pike and his co-workers (Pike et al., 1983; Pike, 1987) (see Appendix). Their method uses the distribution of pertinent reproductive variables to permit cross-cultural prediction of women's cancer incidence. The approach is analogous to estimating changes in coronary heart disease mortality that might result from modification of risk factors for atherosclerosis (Tsevat et al., 1991; Grover et al., 1992).

The model omits consideration of nonreproductive factors (e.g., exercise and dietary fat), but nevertheless suggests major differences in women's cancer frequency. American women in their sixties who have had some education beyond high school and who have not used COCs might have incidences of breast, ovarian, and endometrial cancer 128, 21, and 287 times, respectively, the corresponding incidences for women of similar age living in the late Paleolithic. [About 9% of hunter-gatherers reach age 60 and beyond (Howell, 1979; Table 4).] Such numbers imply epidemiological precision unjustified by the available data. Nevertheless, they suggest that the incidence of women's cancers today is far higher than for ancestral women, whether the difference be 10-fold or 200-fold. The prevalence of these malignancies among current lower-risk popu-

lations (e.g., Chinese and Japanese) appears to be intermediate between the likely basal (Paleolithic) level and that observed in fully Westernized nations. The evidence that oral contraceptives protect against ovarian and endometrial malignancies has become very convincing, so women who have used COCs for prolonged periods should be at substantially reduced risk for these tumors (Table 4; Cancer and Steroid Hormone Study, 1987; Villard-Mackintosh et al., 1989).

Our remote ancestors' presumptive diet, exercise, and body composition anticipated widely advocated broad-spectrum health promotion goals whose achievement might reduce the frequency of women's cancers, but redirecting current reproductive patterns toward those of our ancestors would be highly controversial. While more nursing stands a reasonable chance of popular acceptance, the adverse sociodemographic effects of early first birth and increased parity would probably more than offset the potential benefit of reducing women's cancer frequency.

It might still be possible to approximate key features of our ancestral endocrine milieu without changing current birth patterns. A potential approach would entail exogenous hormonal treatment (Marshall, 1993) along one or more of three separate therapeutic avenues:

(1) Puberty might be delayed by administration of either progesterone or gonadotropin-releasing hormone agonists.

(2) Animal experiments have shown that, after menarche, high doses of estrogen and progesterone can induce maturation of breast ductal epithelium (similar to that which accompanies a first full-term pregnancy), thereby reducing susceptibility to carcinogenesis. This transformation has been achieved without harming subsequent reproduction and/or lactation (Russo et al., 1982; Grubbs et al., 1985).

(3) Birth control pills that can lower serum estrogen to levels approaching those found in hunter-gatherer women are already in early clinical trials (Henderson et al., 1993).

This approach sounds radical (though no more than widespread oral contraception did 30 years ago), but its end result might be to recreate the microanatomical and hormonal milieu for which human physiology has been designed through evolution. It is in fact our current lifestyle and its effect on reproductive experience that is unnatural. Nevertheless, investigation along these lines needs to proceed in parallel with a societal debate about the desirability of such measures.

During the past 60 years improvements in diagnosis and treatment have had no effect whatsoever on breast cancer mortality (Boring et al., 1992). The evolutionary paradigm suggests, however, that prevention based on interventional endocrinology might reduce the incidence of women's cancers to a basal or "natural" level much below that currently reported by any of the world's Western nations—from one fifth to possibly one hundredth the rates now prevalent in the United States.

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APPENDIX

Mathematical models for the incidence rates of cancers of the breast, endometrium and ovary

The age-specific incidence rates of breast, ovarian and endometrial cancers can be approximated by the equation

$$I(t) = a[d(t)]^k,$$

where $I(t)$ is the probability of being diagnosed with the particular cancer within a year at age t , a is a constant specific to the cancer site, $d(t)$ is the "relevant age" of the tissue in question, and k varies with the specific cancer under consideration (4.5 for breast, 4.0 for ovarian, and 6.0 for endometrial cancer) (Pike, 1987). The relevant age, $d(t)$, of different organs is determined by assuming differing rates of aging (closely related to cell proliferation rates in the relevant organ) at different times in a woman's life, particularly during the pre- and postmenopausal periods, and for breast cancer before and after first birth.

For the breast, aging begins around menarche (m) and continues at rate $f_{b,nul}$ until first full-term pregnancy (g), after which it diminishes abruptly to rate $f_{b,par}$. Ten years before menopause (last menstrual period, l) the aging rate begins to taper gradually, ultimately reaching rate $f_{b,post}$ at the last menstrual period. The model incorporates a constant, b , which represents a one-time increase in $d(t)$ associated with the age at first full-term pregnancy. Dur-

ing periods of lactational amenorrhea the rate is as in the postmenopausal period, that is, $f_{b,post}$.

For the ovary, aging is assumed to begin at menarche and to proceed at rate $f_{o,pre}$ until the last menstrual period, when it diminishes abruptly to rate $f_{o,post}$. Between menarche and the last menstrual period there are times during which the ovaries are protected: during pregnancy and postgestational anovulation [and also when oral contraceptives (OCs) suppress ovulation]. For these "protected times" ovarian aging progresses at rate $f_{o,post}$.

For the endometrium, aging is assumed to begin at menarche and to proceed at rate $f_{e,pre}$ until the last menstrual period, when it diminishes abruptly to rate $f_{e,post}$. Between menarche and the last menstrual period there are times during which the endometrium is protected: during pregnancy and postgestational anovulation (and also when OCs suppress ovulation). During pregnancy endometrial cell proliferation is effectively zero; during postgestational anovulation endometrial cell proliferation is as in the postmenopausal period, that is, $f_{e,post}$; and during OC use it is estimated to be approximately $0.38f_{e,pre}$ (Pike and Spicer, 1993).

These models allow comparison of cancer rates between populations with varying reproductive and hormonal (steroid) experience.

The comparison between educated US women and hunter-gatherers is based on the following data assumptions (all data in years):

	Educated US women	Hunter- gatherers
menarche (m)	12.50	16.1
first full-term pregnancy (g)	26.50	19.5
parity (p)	1.80	5.9
last menstrual period (l)	50.50	47.0
lactational amenorrhea (n)	0.25	2.0
oral contraceptive use (c)	3.00	0.0

BREAST CANCER:

$$d(t) = f_{b,nul}(g - m) + b + f_{b,par}[(1 - 10) - g - p \times n] + f_{b,post} \times p \times n + 0.5(f_{b,par} + f_{b,post}) \times 10 + f_{b,post}(t - 1).$$

	Educated US women	Hunter- gatherers
$f_{b,nul}$	1.000	0.80
$f_{b,par}$	0.700	0.56
$f_{b,post}$	0.105	0.00
b	2.200	1.76

$d(60) = 30.750 - 10.47 = 20.28$
 relative risk (RR) = $(30.75/10.47)^{4.5} = 128$
 relative cumulative risk to age 60 = 114

Choice of parameters: Parameters for US women estimated from incidence data as described by Pike (Pike et al., 1983; Pike, 1987). The $f_{b,nul}$, $f_{b,par}$, and b parameters for hunter-gatherers are reduced by 20% from the figures for US women to agree with the approximately 20% lower estrogen levels found in premenopausal low-risk Asian women. The $f_{b,post}$ parameter for hunter-gatherers is assumed to be zero as found in low-risk Asian women (Pike et al., 1983; Pike, 1987).

OVARIAN CANCER:

$$d(t) = f_{o,pre}(1 - m - p \times 0.75 - p \times n - c) + f_{o,post}(p \times 0.75 + p \times n + c) + f_{o,post}(t - 1).$$

	Educated US women who have not used OCs	Hunter- gatherers
$f_{o,pre}$	1.00	1.00
$f_{o,post}$	0.09	0.09
$d(60)$	37.22	17.31

RR = $(37.22/17.31)^4 = 21$
 relative cumulative risk to age 60 = 24

Choice of parameters: Parameters for US women estimated from incidence data as described by Pike (Pike et al., 1983; Pike, 1987). Parameters for hunter-gatherers are assumed to be the same as for US women; this assumption probably overestimates risk to hunter-gatherers as there is epidemiologic evidence that the low risk of Asian women cannot be completely explained by late menarche, fertility, and breast-feeding.

ENDOMETRIAL CANCER:

$$d(t) = f_{e,pre}(1 - m - p \times 0.75 - p \times n - c) + f_{e,post} \times p \times n + 0.38(f_{e,pre} \times c) + f_{e,post}(t - 1).$$

	Educated US women who have not used OCs	Hunter- gatherers
$f_{e,pre}$	1.00	1.00
$f_{e,post}$	0.15	0.00
$d(60)$	37.69	14.68

RR = $(37.69/14.68)^6 = 287$
 relative cumulative risk to age 60 = 240

Choice of parameters: Parameters for US women estimated from incidence data as described by Pike (Pike et al., 1983; Pike, 1987). The $f_{e,post}$ parameter for hunter-gatherers is assumed to be zero, consonant with their assumed low rate of conversion of adrenal androgens to estrogens as found in low-risk Asian women.