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Height of Women, Twinning and Breast Cancer: Epidemiological Evidence of a Relationship

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Abstract. A comparison was made of the stature of women, twinning rates, and breast cancer mortality for 32 countries. As height increased, so did twinning and breast cancer mortality ($P < 0.005$). Dizygotic twinning and breast cancer increased sharply with the mean height of the female population. With due caution in drawing causal inferences when uncontrolled confounding variables are present, it is suggested that these findings are an evolutionary consequence of the high mortality found in twin pregnancy.

Key words: Twinning rates, Height of women, Breast cancer, Gonadotrophins, Perinatal mortality

INTRODUCTION

Dr. Joseph Clarke, in Dublin in 1785, observed that "when a woman conceives twins it becomes peculiarly fatal both to her and her offspring" [17]. He noted a four fold increase in maternal mortality and a doubling of perinatal deaths. Has so fearful a toll, acting over many generations, had evolutionary consequences in man? The selection pressure against a hereditary [12,29] twinning tendency must surely have been intense.

The first clue comes from Tchouriloff in Paris in 1877 [71] who examined statistics on twinning in Europe. Using exemptions from military service on grounds of height as an index of stature, he found that as height increased so, too, did twinning, but *pari-passu* stillbirths in twins fell. Overall, the stillbirth rate in twins was four times that in singletons and a doubling of the twinning rate was accompanied by a halving of the twin stillbirth rate. He considered there were physiological reasons linking the twinning trait to the ethnic characteristic of height. Analogous studies in animals support this.

A relationship between body size and litter size has been shown in mice, rabbits, pigs and sheep; in some wild mammals those of the species living in colder climates tend to be bigger and have larger litters [48]. Early in the nineteenth century Bassi [7] described his method of promoting twinning in sheep by breeding from those "of greater corpulence, of best constitution and being, above all, copiously fed." Subsequent research has proved him exactly right. Experimental work in sheep has confirmed that mothers of twins are fatter and of larger skeletal size [73], that flushing (ie, feeding up) increases the twinning rate [82] and that maternal nutrition has a profound effect on fetal outcome, particularly in twins [81].

The second clue comes from Dublin. In reporting that Ireland had the highest national twinning rate in the world, Dean and Keane [22] pointed out that the Japanese had low rates of twinning and of breast cancer, both of which were under the influence of pituitary gonadotrophins. (Interestingly, the Irish propensity for record twinning levels had first been documented by Dr. Joseph Clarke's son-in-law, Dr. Robert Collins, in 1835 [18]).

These leads suggest the hypothesis that short women have less breast cancer because their twinning tendency has been suppressed through lowering of their gonadotrophin levels.

MATERIALS AND METHODS

A search was made of demographic and mortality data published by the United Nations [75] and World Health Organization [88] to find countries reporting national rates for twinning and breast cancer. Twinning rates were given as twin births per 1,000 births for 1980 or the most recently available previous year. Mortality rates for malignant neoplasm of the female breast per 100,000 of the standard population were for years between 1980 and 1984. The rates had been age-standardized using the "World" population age structure [84] as the standard. Corresponding mean heights of adult females were taken from surveys in the periods 1950 to 1965 [54] and 1960 to 1973 [28]. Most were derived from measurements of several thousand subjects and should be representative national samples (eg, Japan 500,000 subjects) but the Finnish (120 subjects) and Romanian (174 subjects) averages have more likelihood of sampling error.

The dizygotic (DZ) and monozygotic (MZ) fractions of the twinning rate can be found by Weinberg's method [86]. The sex combination of the twin pairs must be known but few countries publish this information. Several possible sources of error have been suggested in Weinberg's method [1,38,65] but for large, unbiased populations it should be accurate [1,12,13]. There is some evidence of MZ variation with maternal age [37,64], parity [31,51] and over time [9,25]. These apparent variations may be due to the MZ rate mimicking the DZ rate or to slight overestimation of the MZ rate [40]; they are, in any case, very small compared with the DZ changes. For this study, the MZ rate is taken to be constant at 8 per 1,000 births and to be independent of race, age or parity [12,57,66]. Differences in the twin rates are therefore attributable to the DZ fraction.

The data were examined by linear regression analysis; product moment correlation coefficients were calculated and the variance ratio, F, used as a test of significance [3].

RESULTS

Thirty-two countries were identified for which height and twinning rates were available. Breast cancer rates were found for twenty-seven of them. They are listed in order of height in Table 1.

Table 1 - Height of women, twin births, and breast cancer by country

Country	Mean height of adult women (cm)	Twin births (per 1,000)	Breast cancer (Deaths per 100,000)
Denmark	167.0	19.92	24.7
Norway	166.6	18.08	16.7
Netherlands	166.3	20.48	26.4
Finland	165.0	21.32	16.8
Switzerland	165.0	18.31	24.5
Germany F.R.	164.9	18.62	21.6
New Zealand	164.3	19.47	27.1
Czechoslovakia	164.0	18.18	20.2
U.S.A.	163.8	19.13	22.1
Germany D.R.	163.4	16.70	
U.K. England & Wales	163.6	18.74	28.4
Belgium	163.1	18.61	
Sweden	162.9	17.82	18.6
France	162.6	17.60	19.2
Australia	161.9	19.12	20.4
Poland	161.0	17.66	15.2
Yugoslavia	160.9	20.14	13.0
Hungary	160.8	20.85	20.2
Bulgaria	160.2	13.46	13.7
Puerto Rico	160.0	14.40	9.1
Ireland	159.8	23.22	24.5
Italy	159.4	17.62	19.0
Greece	159.1	17.25	15.6
Canada	159.0	18.11	23.4
Costa Rica	158.3	10.19	11.0
Spain	157.3	16.64	
Romania	157.1	15.88	13.3
Cuba	156.5	14.93	14.9
Hong Kong	156.1	13.17	9.2
Japan	154.3	11.98	5.8
Libya	153.4	11.51	
Chile	151.7	13.72	

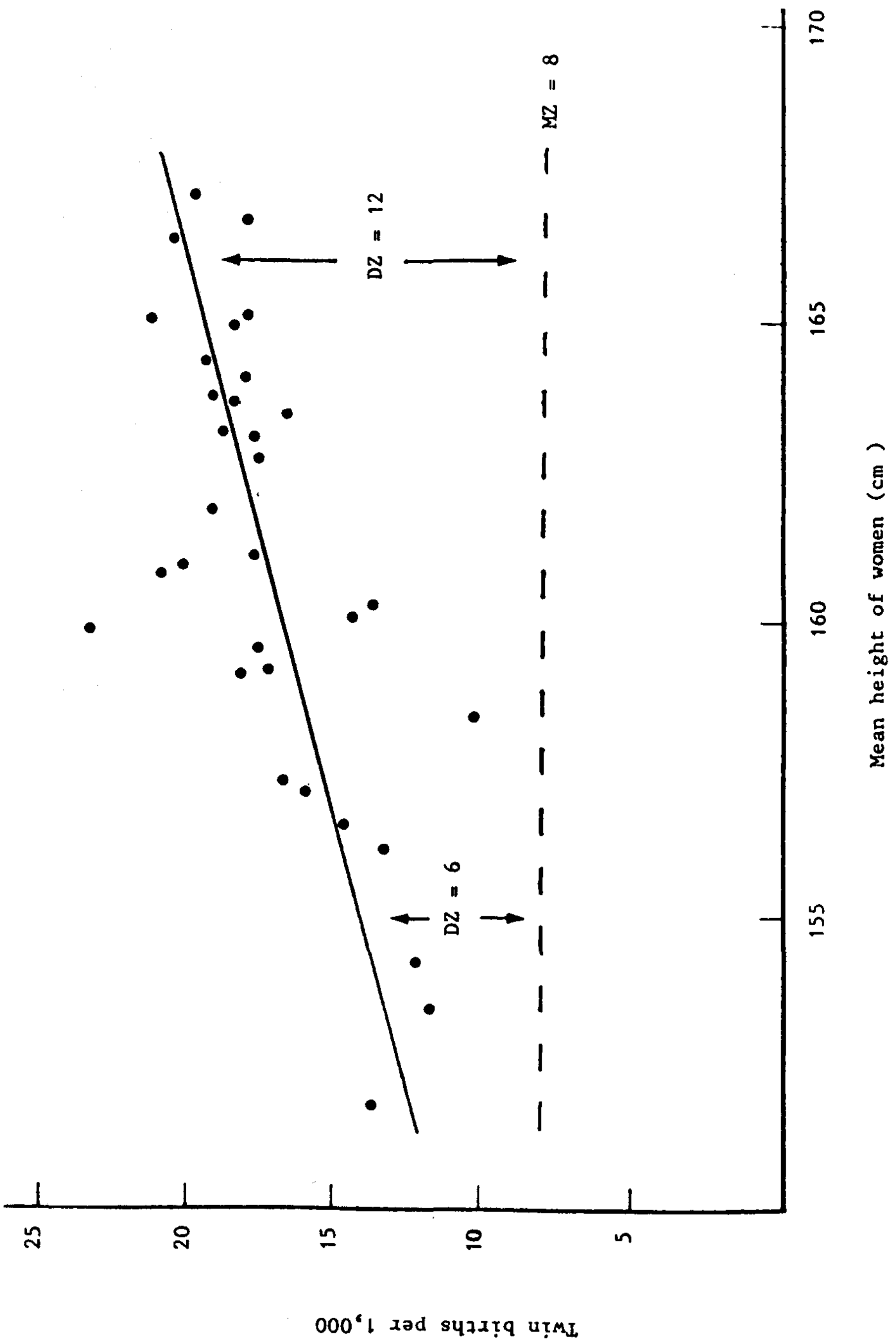

Fig. 1. Twinning rate by mean height of the female population, 32 countries.

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Twenty-one of the countries are in Europe and eight of the remainder have populations with considerable European ancestry. Only Libya, Hong Kong and Japan have distinctly non-European populations, while the Latin American countries have elements of Indian (Mongoloid) descent.

The tallest populations were found in northern Europe (Denmark 167.0 cm) and the shortest in Chile (151.7 cm), Libya, Japan and Hong Kong. The highest twinning rates were in Ireland (23.22 per 1,000), Finland and Hungary, and the lowest in Costa Rica (10.19 per 1,000), Libya, Hong Kong and Japan. Peak breast cancer deaths were in the United Kingdom (28.4 per 100,000), New Zealand, the Netherlands and Denmark; the lowest mortality was in Japan (5.8 per 1,000), Hong Kong, Puerto Rico and Costa Rica. Mortality rates were not available for Libya or Chile.

Figure 1 is a scattergram of twinning rates against mean height. The solid line shows the regression of twinning on height. There is a highly significant positive correlation ($P < 0.005$). The slope of the curve represents the trend of DZ births. By illustrating the MZ births (broken line), the proportions of each zygosity can be seen. At a female population mean height of about 158.5 cm there would be equal numbers of MZ and DZ twins (both 8 per 1,000). Above 158.5 cm most would be DZ and below this mostly MZ. A sharp gradient is seen, the DZ rate doubles from 6 per 1,000 to 12 per 1,000 with an increase in height of 11 cm from 155 to 166 cm. The twinning rate (TR) is given by the regression equation ($y = \alpha + \beta x$):

$$\text{TR} = -67.77 + 0.35x \qquad \text{(where } x \text{ is height).}$$

Figure 2 shows the regression of female breast cancer mortality on mean height. The regression line demonstrates a marked increase with height. The breast cancer mortality (BC) is given by the regression equation:

$$\text{BC} = 174.76 + 1.196x.$$

Table 2 gives the correlation coefficients of the variables with their F ratios and significance levels. Height was correlated equally ($r = 0.69$) with twinning and breast cancer. Twinning and breast cancer were highly correlated ($r = 0.74$). All the correlations were very highly significant ($P < 0.005$).

DISCUSSION

A clear trend of increasing twinning and breast cancer with height has been demonstrated internationally. In countries with a female population of short stature both twinning rates and breast cancer rates tend to be low. Countries with tall women tend to have high rates of twinning and breast cancer. The associations are statistically highly significant, but two cautions must be mentioned. The data have inherent limitations and association is not causation.

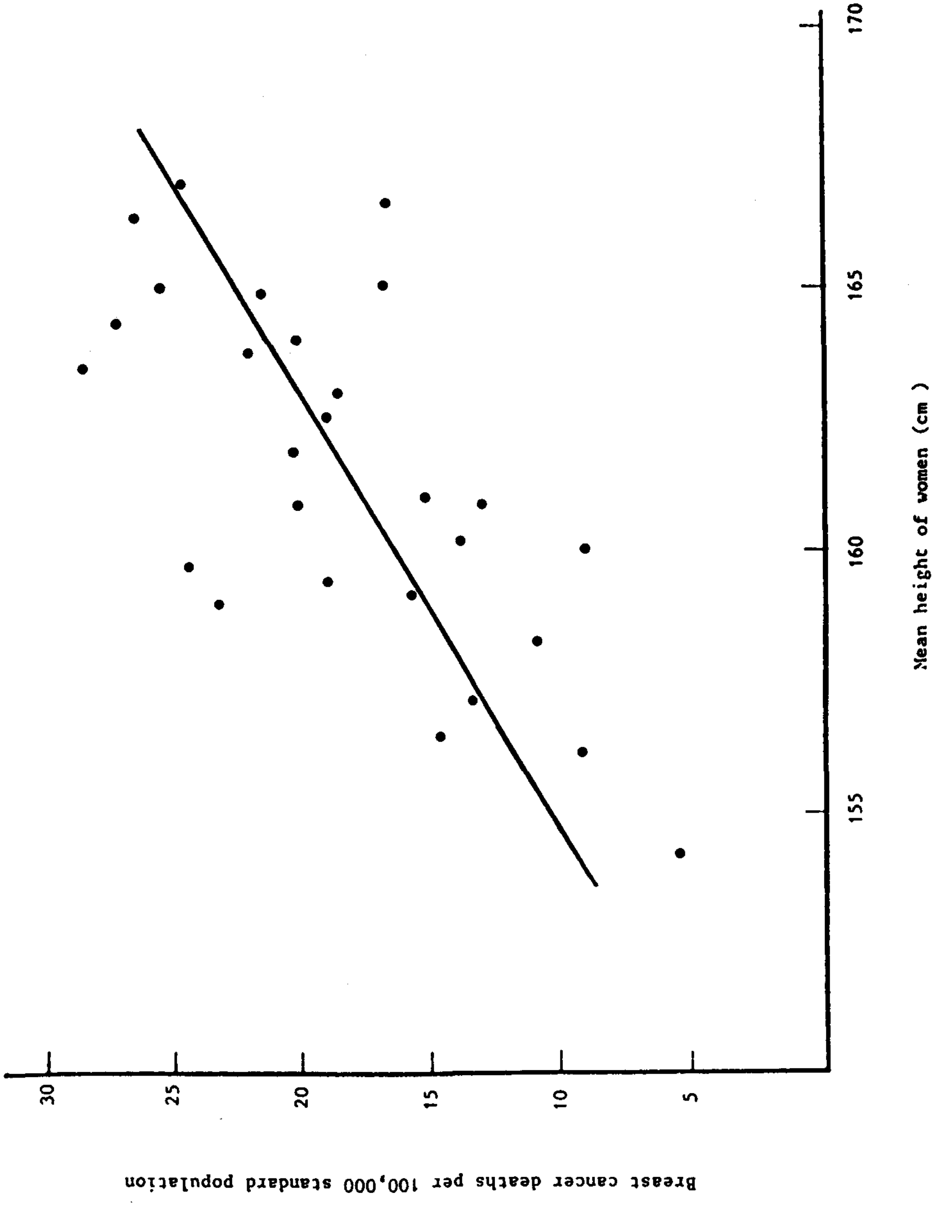

Fig. 2. Carcinoma of the female breast, age standardized mortality by mean height of the female population, 27 countries.

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Ideally for this type of enquiry, anthropometric and disease incidence data for the same cohort of women who contributed the twinning rate should be used, but such data are not available. No allowance was made for secular trends in twinning [25,39], height [70] or breast cancer [47] except to use data as nearly contemporaneous as possible within each of these categories. No adjustment could be made for parity or maternal age which are known to influence twinning rates [83]. It is likely, however, that these deficiencies would dilute a real relationship rather than produce a factitious one. How does this accord with earlier studies?

Table 2 - Correlation coefficients of height of women, twinning and breast cancer

	Twinning	Breast cancer
Height	0.69 F = 26* (df 1,31)	0.69 F = 22.5* (df 1,26)
Twinning	1	0.74 F = 30* (df 1,26)

* $P < 0.005$

Geography

Geographic variation in twinning has long been recognised. International comparisons at various times have shown high rates in Ireland [18,22], Hungary [8], Sweden and Finland [27,33,42,86], Denmark [21,33], Russia [21], Norway [74], Prussia [77,86], Belgium [35] and Nigeria [62]. Low rates have been found in Japan [37,43], Korea [43], Formosa [43], Taiwan [85], Colombia [33], Paraguay [33], Greece [33], Singapore [56], Mexico [39] and Spain [42]. Regional variation has been seen within Norway [74], Sweden and Finland [27], Italy [63], Nigeria [58], the United States [35] and across Europe [11]. Different twinning rates are shown by Blacks, Whites [34,35,69], Japanese and Chinese [66] in America, and by major tribal groups in Nigeria [58]. Two broad generalisations have been drawn, first that twinning rates are highest in Blacks, intermediate in Europeans and lowest in Mongoloid peoples and second that there is a gradient of increasing frequency from South to North in Europe. The data in this study are in accord with both these generalisations except that Blacks were not separately represented.

Das [21] and Weinberg [86] considered and dismissed the possible influence of latitude and climate asserting that twinning was a racial characteristic though Weinberg held that the influence of height and fertility could not be assessed on the information then available. However, Kamimura [41] observed that in Japan as latitude increased and mean temperature fell the DZ rate increased. He supported a climatic influence.

These variations have been maintained over long periods in spite of secular trends. Data from 1745 in Ireland [17,18,21], 1749 in Sweden [26], 1826 in Prussia [77], 1851 in Hungary [8] and 1904 in Japan [43] confirm the present pattern. This long-term stability suggest a constant influence. Many factors which may have caused variation in twinning have been studied including maternal age and parity [83], fertility and fecundity [24,86], environmental changes [39], psychosocial influences [63] and prenatal loss [44]. While these factors may have caused movements in twinning rates they would not have exerted a constant influence for more than a century. Could height be a determining factor?

Height

The DZ rate is shown here to increase very sharply with stature. A gradient of twinning with maternal height has been shown in England [19], Scotland [19,20,49,59], Nigeria [59] and Norway [74] which persists after standardization for age and parity [61] and is due to mothers of DZ twins [19]. This may have reflected better nutrition in taller mothers in Nigeria [59,61] but no trend with social class, and presumably better nourishment, was found in Scotland [14]. Nutrition, weight and social class are potential confounders. One study found that weight could explain the effect of height but not vice versa [36]. Malnutrition reduced DZ twinning in wartime Europe [10] while a rising plane of nutrition optimizes twinning in sheep [82].

Reproductive performance is best in tall women [6], short stature and poor performance may be due to stunting of growth caused by inadequate feeding. Maternal food intake and energy reserves are major determinants of fetal growth, an extra 1,200 kJ per day has been advised during pregnancy [89]. The prevalence of low birth weight is inversely related to maternal body mass index in singleton pregnancy [76] and this effect is likely to be exacerbated with the additional demands of twins [5]. Of the 32 countries in this study, all except two had a daily calorie supply per capita of 114% or more of requirements (Chile 109%, Puerto Rico unknown) [87] so underfeeding should not be a serious confounder between countries.

Breast Cancer

The correlation coefficient of 0.69 for height and breast cancer mortality for 27 countries in the present study is higher than the 0.61 found in a previous analysis of 26 countries [32] which showed a higher correlation with weight (0.68). The same analysis also showed a correlation of 0.78 between height and total fat intake.

The etiology of breast cancer is multifactorial and includes ovarian activity [47]. International comparisons of variables show correlations, amongst others, with height, weight, fat consumption and also with gross national product, which may reflect another correlate of economic development [4,32]. In Japan and the Netherlands there is a clear gradient of breast cancer incidence with height; over half the difference in incidence between the countries can be attributed to differences in height, and slightly less to differences in weight [80]. Although height and weight are pronounced risk factors, the evidence for their relative importance is not consistent [45,79]. However, for postmenopausal women the effect of height accounts for all the risk attributable to body mass [78].

There is a definite gradient of breast cancer mortality with social class [46]. Mortality increases regularly with higher social class, whereas the reverse is true for cancer of all sites combined. This would not be expected to affect international comparisons unless the distribution of the variables with class differed between countries.

CONCLUSION

If height, twinning and breast cancer are correlated, is it biologically plausible to link all three? It may be that height is acting as a proxy for another aspect of body build. It could be a marker for body mass or pelvic diameter. Since this cannot be established from the present data it suffices to take height as the explanatory variable, bearing in mind that other features of build may be involved. It is assumed that DZ twinning is under genetic control [12].

Population studies [9,23] show a five-fold increase in perinatal mortality in twins. This high mortality is, itself, inversely related to maternal height [2]: between 3 and 5 pounds birthweight, mortality was four times higher among twins of short than of tall women. The main cause is preterm delivery and low birthweight [72]. Birthweight increases with maternal height [15, 49] and this association is sharper in twin pregnancy [52]. With increasing height of the mother the length of gestation increases in twin but not singleton pregnancies [53], and birthweight increases with length of gestation [16].

Given this mortality, there must have been evolutionary selection pressure against twinning, which would have been most marked in short women and least in tall women. This could have been mediated via the pituitary. Milham [55] hypothesized that DZ twinning could be explained by multiple ovulation induced by excessive pituitary gonadotrophins and it is known that treatment of infertility with gonadotrophins leads to multiple births [30]. So, selection pressure might have acted by lowering maternal gonadotrophins. This is consistent with the findings that Japanese women have a low output of gonadotrophins [68] and that mothers of twins have high levels of FSH [50,60] and LH [50]. Thus it is reasonable to postulate that the very high mortality due to twinning caused the suppression of the DZ trait in short women. As a secondary consequence, breast cancer, which is hormone-dependent [47], was similarly reduced. And there could well be other physiological or pathological sequelae.

This twinning-gonadotrophin-breast cancer nexus was alluded to by Dean and Keane [22] and developed independently by Wyshak [90] and Short [67]. Wyshak proposed that mothers of DZ twins would have a higher incidence of breast cancer than mothers of singletons, but a cohort study did not support this, although there was an excess incidence of pancreatic cancer, which may be influenced by gonadotrophins [90,91]. Short [67] linked testis size, ovulation rate and breast cancer in suggesting reduced DZ twinning as a contributory factor in low Oriental breast-cancer rates.

Although the confounding variables of nutrition and body weight cannot be completely eliminated, the data in this analysis support the hypothesis that short stature is causally associated with a low incidence of dizygotic twinning and breast cancer.

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