

RESEARCH POINTERS

Lifestyle, hormones, and risk of breast cancer

Nutritional status influences ovarian steroid hormones and breast cancer incidence

Institute of Public Health, Jagiellonian University, Grzegorzeczka 20, 31-531 Krakow, Poland

Grażyna Jasieriska assistant professor, reproductive biology

Institute of Community Medicine, Norwegian Cancer Society, Faculty of Medicine, University of Tromsø, 90037 Tromsø, Norway

Inger Thune associate professor, cancer epidemiology

Correspondence to: G Jasieriska jasienska@post.harvard.edu

BMJ 2001;322:586-7

The incidence of breast cancer is much higher among women in industrialised countries than among women in countries with more traditional lifestyles. Energy intake, energy expenditure, and energy balance may influence ovarian physiology and the concentrations of ovarian oestrogen and progesterone produced during the menstrual cycle. Oestrogen and progesterone are hypothesised to play a crucial part in the development of breast cancer in women.¹ Women from populations with a high risk of breast cancer are expected to have comparatively high concentrations of ovarian steroid hormones.

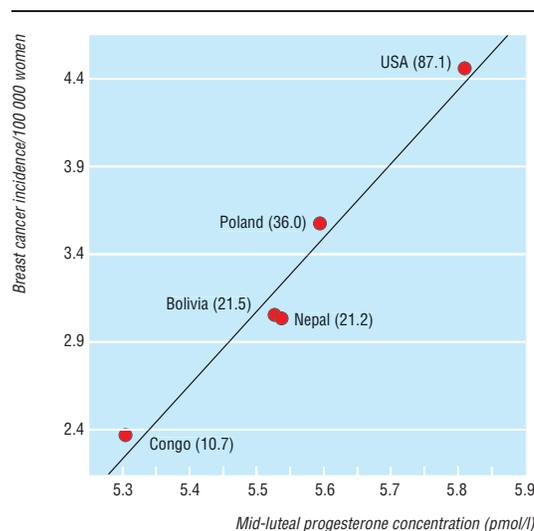
Methods and results

Saliva samples were taken previously from women in Bolivia, the Democratic Republic of Congo, Nepal, Poland, and the United States.² Samples were collected daily during at least one menstrual cycle from women 25 to 35 years old, and progesterone concentrations were analysed by radioimmunoassay.² Mean concentrations were calculated for the fifth to ninth days preceding the start of the next cycle (mid-luteal phase); these are the days with the highest progesterone concentrations.²

The relation between these concentrations and the incidence of breast cancer in each country was investigated. The data on cancer incidence were obtained from the Globocan database of the International Agency for Research on Cancer (www-dep.iarc.fr/dataava/globocan/globoJava.html). The populations studied in this analysis are the only ones for which reliable values of ovarian progesterone are available. All variables used in this study were transformed to natural logarithms before the correlation analyses were performed.

Higher concentrations of ovarian progesterone in the mid-luteal phase were strongly associated with an increasing incidence of breast cancer ($r^2 = 0.968$, $P = 0.0025$) (figure): an increase in progesterone concentration of < 70% coincided with a more than 8-fold rise in cancer rate. This pattern confirms the expected positive relation between concentrations of ovarian progesterone and incidence of breast cancer in these populations.¹

Mean total energy intake was used as a crude indicator of the relative energy status of a population and its relation with progesterone concentrations was examined. The mean values used in this analysis came from the food balance sheets of the Food and Agriculture Organisation (<http://apps.fao.org/page/collections>); values used were 7.6 MJ/day for the Congo, 9.2 MJ/day for Bolivia, 9.6 MJ/day for Nepal, 14.0 MJ/day for Poland, and 15.3 MJ/day for the United States. These values were positively and significantly correlated with concentrations of ovarian progesterone ($r^2 = 0.818$, $P = 0.035$). Thus, poor energy status in a population is associated with impaired ovarian function in women.



Relation between mean concentrations of progesterone in saliva during mid-luteal phase and age standardised (world population) rates of breast cancer per 100 000 women. Cancer incidence for each country is shown in parentheses. Both variables transformed to natural logarithms

Clinical studies have shown that restricting energy intake frequently leads to recurring suppression of reproductive function. Such suppression ranges from reduced steroid production and anovulatory cycles to total amenorrhoea when conditions become severe. In these circumstances the lifetime production of ovarian steroid hormones is curtailed. In contrast, when the available energy is virtually unlimited women have frequent ovulatory menstrual cycles characterised by high hormone concentrations.

Comment

There is an important link between the risk of breast cancer and the nutritional status of a population; this link is mediated by ovarian sensitivity to environmental conditions. Although evidence of the link between ovarian function and breast cancer risk is based on the study of a limited number of populations (and important covariates such as age at menarche, parity, and breastfeeding have not been taken into account), the strength of the relation strongly suggests that it is an important biological phenomenon. Furthermore, since ovarian function responds to nutritional status, the risk of breast cancer may be modified if changes are made in a woman's lifestyle.³ An increase in physical activity and decrease in caloric intake may thus lead to lower concentrations of progesterone and oestrogen, resulting in a reduction in breast cancer risk.

We thank Peter T Ellison of Harvard University; owing to his understanding of the need to study the reproductive function of

women worldwide, reliable data on hormone concentrations exist.

Contributors: GJ wrote the paper, compiled the data on hormone concentrations, and is guarantor for the paper. IT provided the epidemiological data and co-edited the paper.

Funding: Norwegian Cancer Society grant number TP-49258/001.

Competing interests: None declared.

- 1 Jasienska G, Thune I, Ellison PT. Energetic factors, ovarian steroids and the risk of breast cancer. *Eur J Cancer Prev* 2000;9:231-9.
- 2 Vitzthum VJ, Ellison PT, Sukalich S, Caceres E, Spielvogel H. Does hypoxia impair ovarian function in Bolivian women indigenous to high altitude? *High Altitude Med Biol* 2000;1:39-49.
- 3 Friedenreich CM, Thune I, Brinton AA, Albanes D. Epidemiologic issues related to the association between physical activity and breast cancer. *Cancer* 1998;83(suppl):600-10.

(Accepted 13 December 2000)

RESEARCH POINTERS

Light eye colour linked to deafness after meningitis

Bacterial meningitis is the most common cause of profound deafness acquired in childhood. Previously there have been no strong indicators of why some survivors of meningitis experience hearing loss whereas others recover fully.

The link between pigmentation and damage to hearing after exposure to ototoxic substances and noise is well documented. People with brown eyes are more likely to experience hearing loss after exposure to cisplatin. It is assumed that people with dark eyes also have more melanin in the inner ear than those with light eyes, and melanin causes the retention of ototoxic derivatives within the cochlea.¹ A higher melanin content in the cochlea also protects against the effects of noise; those with dark eyes are less likely to develop hearing loss associated with noise.²

Participants, methods, and results

Eye colour was examined in 133 deaf patients with cochlear implants, either by the author's direct observation or by requesting the information by mail. Results were obtained for 130 patients aged from 2 to 80 years (mean 28 years); three patients failed to reply after two letters. The classification of eye colour is subjective; shades of blue, green, grey, and hazel are difficult to distinguish. The classification I used was therefore simply "dark" or "light." "Dark" included pure brown eyes, usually of non-white people, and all other shades of brown. "Light" included blue, green, grey, and hazel eyes.

Overall, 32 patients were deafened by meningitis (table). Of the 98 patients whose deafness was not due to meningitis, 26 (27%) had dark eyes and 72 (73%) had light eyes. This is almost identical to figures obtained from the National Study of Hearing (A Davis, personal communication). From that sample of 1598 adults in the United Kingdom, 447 (28%) had dark eyes and 1151 (72%) had light eyes.

Only two (6%) of the patients in the meningitis group, however, had dark eyes, with 30 (94%) having light eyes. The difference in proportions of eye colour between the survivors of meningitis and the UK adult population was significant. The odds ratio showed that people with light eyes were 5.8 times as likely to be deafened by meningitis than those with dark eyes (95% confidence interval 1.4 to 24.4).

Types of meningitis causing deafness in 32 patients

Type of meningitis	Number of patients
Pneumococcal	20
<i>Haemophilus influenzae</i>	3
Meningococcal	2
Tuberculosis	2
Streptococcal	1
Bacterial, unknown type	1
Viral	1
Unknown	2

Comment

People with light eyes are more likely to be deafened by meningitis than those with dark eyes. I propose that a higher melanin content protects the inner ear from damage caused by meningitis. However it is possible that the data are misleading. Perhaps people with light eyes are more vulnerable to meningitis or those with dark eyes are more likely to die from meningitis, thus skewing the data for eye colour in the survivors. There is much published evidence that black people have a higher incidence of meningitis than white people,³ although the reasons for this may be unrelated to pigmentation. Further research may suggest a genetic basis; perhaps the genes encoding eye colour are in linkage disequilibrium with the genes determining the inflammatory response to infection.

I thank ME Lutman for advice, RL Booth for statistics assistance, G Jones for microbiology input, and GP Clarke for initial motivation of my interest in this topic.

Funding: None.

Competing interests: None declared.

1 Wendell Todd N, Alvarado CS, Brewer DB. Cisplatin in children: hearing loss correlates with iris and skin pigmentation. *J Laryngol Otol* 1995;109:926-9.

2 Barrenäs M-L, Lindgren F. The influence of inner ear melanin on susceptibility to TTS in humans. *Scand Audiol* 1990;19:97-102.

3 Henneberger PK, Galaid EL, Marr JS. The descriptive epidemiology of pneumococcal meningitis in New York City. *Am J Epidemiol* 1983;117:484-91.

(Accepted 23 November 2000)

Correction

Systematic review of long term anticoagulation or antiplatelet treatment in patients with non-rheumatic atrial fibrillation

In this paper by Taylor et al (20 January, pp 321-6) the name of the drug used in antiplatelet treatment should have been indobufen, not indoprofen. Indoprofen was withdrawn from use worldwide after reports of carcinogenicity in animal studies.

People with light eyes are more prone to deafness after meningitis than those with dark eyes

Hearing and Balance Centre, Institute of Sound and Vibration Research, University of Southampton, SO17 1BJ

Helen E. Cullington
audiological scientist

Correspondence to:
H E Cullington
hec@isvr.soton.ac.uk

BMJ 2001;322:587