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RESEARCH POINTERS

Mortality from cardiovascular disease more than 10 years after radiotherapy for breast cancer: nationwide cohort study of 90 000 Swedish women

Increased cardiovascular mortality more than 10 years after diagnosis of breast cancer is compatible with radiotherapy causing a substantial hazard

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During radiotherapy for breast cancer there is often some irradiation of the heart and major blood vessels, which could increase cardiovascular mortality many years later.[1–3] The dose of radiation to the heart is generally higher when the left rather than the right breast is affected. Therefore, indirect evidence on the magnitude of any risk is available where the tumour laterality (left or right breast) can be linked to subsequent cardiovascular mortality.[1 2] Studies of the survivors of the atomic bombing of Japan who received single doses to the whole body of 0-4 Gy show that the cardiovascular disease risk is dose related and increases by about 14% per gray.[4]

Participants, methods, and results

Since 1970, the nationwide Swedish cancer registry has recorded the laterality of breast cancers but not the use of radiotherapy. Unpublished data from regional Swedish registries suggest that about 30% of women with early breast cancer during the 1970s and early '80s received radiotherapy. We linked registry records (1970-96) with national mortality records. The study was approved by the ethics committee of the Karolinska Institute.

After we excluded women whose cancer was diagnosed at autopsy or outside Sweden and those with previously registered cancers (except squamous cell skin cancer), 89 407 women aged 18-79 with unilateral breast cancer remained. We stratified analyses of subsequent mortality in groups of five years by calendar year of diagnosis, time since diagnosis, and age at diagnosis. Stratification by age was necessary because the proportion of left sided tumours increases with age.[5] Each woman's contribution to the person years at risk ran from the date of diagnosis until her date of death, date of emigration, 100th birthday, or 1 January 1997, whichever was earliest. We used Poisson regression to calculate mortality ratios, left versus right, from the numbers of deaths and person years. Ratios greater than one indicate greater mortality in women with left sided tumours than in women with right sided tumours.

Mortality from breast cancer was identical in women with left sided or right sided tumours (table). Mortality from cardiovascular diseases was higher in women with left sided tumours. Little excess occurred in the first 10 years after diagnosis (mortality ratio 1.01; 95% confidence interval 0.96 to 1.07), but later the ratio was 1.10 (1.03 to 1.18; P=0.004), 1.13 (1.03 to 1.25; P=0.01) for ischaemic heart disease (half of all cardiovascular mortality), and 1.08 (0.98 to 1.18) for other cardiovascular deaths (about 30% of which

Mortality ratio for women with left sided breast cancer versus women with right sided breast cancer during and after the first 10 years from diagnosis of breast cancer among 89 407 women registered during 1970-96 at the Swedish cancer registry

	All years	<10 years		≥10 years	
Cause of death (ICD-9 code)	Mortality ratio, left versus right (95% CI)	No of deaths	Mortality ratio, left versus right (95% CI)	No of deaths	Mortality ratio, left versus right (95% CI)
Breast cancer (174)	1.00 (0.98 to 1.03)	21 196	1.00 (0.97 to 1.03)	2714	1.00 (0.93 to 1.08)
Cardiovascular diseases:					
All (390-459, 785, and 798)	1.04 (1.00 to 1.09)*	5 739	1.01 (0.96 to 1.07)	3426	1.10 (1.03 to 1.18)†
Ischaemic heart disease (410-414)	1.06 (1.00 to 1.12)‡	3 078	1.02 (0.95 to 1.10)	1613	1.13 (1.03 to 1.25)§
Other cardiovascular diseases	1.03 (0.97 to 1.09)	2 661	1.00 (0.93 to 1.08)	1813	1.08 (0.98 to 1.18)
Remaining causes	0.97 (0.93 to 1.02)	4 446	0.96 (0.90 to 1.01)	2602	1.00 (0.92 to 1.07)

ICD-9=International classification of diseases, ninth revision.
*P=0.04
†P=0.004
‡P=0.05
§P=0.01

probably involved heart disease). For the remaining causes, mortality in women with left sided tumours did not differ significantly from that in women with right sided tumours.

Most of the late cardiovascular deaths involved women treated for breast cancer in the 1970s, and improvements in radiotherapy techniques since then have tended to reduce radiation dose to the heart. For women treated in the 1980s, however, the cardiovascular ratio, left versus right, was still 1.11 but with a wide 95% confidence interval (0.95 to 1.29).

Comment

A mortality ratio, left versus right, of 1.10 for cardiovascular disease more than 10 years after diagnosis of breast cancer is compatible with a substantial hazard among some of those actually irradiated. For example, if about 30% of women surviving 10 years after breast cancer had been irradiated then a cardiovascular mortality ratio of 1.10 in all women and 1.00 in unirradiated women would suggest a ratio of 1.33 in those irradiated. This could be produced by a 60% increase in late cardiovascular mortality after irradiation for a left sided tumour and a 20% increase after irradiation for a right sided tumour. The confidence interval for the observed ratio of 1.10 is, however, wide, so the true cardiovascular hazard from radiotherapy in the 1970s and '80s remains uncertain.

Contributors: The study was conceived and designed by PH, SD, AE, and FG. The statistical analysis was designed by SD and PMcG and done by PMcG. All authors contributed to the interpretation of the results and the preparation of the manuscript. PH is guarantor for the data; SD and PMcG are guarantors for the statistical analysis.

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Drug points

Thromboembolism associated with the new contraceptive Yasmin

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Our centre, the Dutch spontaneous reporting system for adverse drug reactions, recently received five reports of thromboembolism as a suspected adverse drug reaction to the new oral contraceptive Yasmin (ethinylestradiol and drospirenone).

A 17 year old woman suddenly collapsed and died after taking the contraceptive for six months. Autopsy showed that she had had a massive pulmonary embolism. No obvious risk factors for thromboembolism, such as smoking, a period of long immobilisation, air flights, or concomitant medication, were evident.[1] Because she died suddenly no blood sample was taken. Blood taken from her parents did not test positive for any of the known risk factors: concentrations of protein C and antithrombin III were normal. The activated partial thromboplastin time and partial thromboplastin time were normal, and the existence of factor V Leiden mutation was excluded.

A 28 year old woman changed her oral contraceptive from ethinylestradiol with desogestrel (Marvelon) to ethinylestradiol with drospirenone. Four months later she had thrombosis in one leg and was treated with acenocoumarol. Risk factors or concomitant drugs were unknown.

Another patient, a 45 year old woman, had deep vein thrombosis in one leg after taking ethinylestradiol with drospirenone for two months, as did a 50 year old woman who took the contraceptive for three months. A 35 year old woman had pulmonary thrombosis 17 days after she started taking the contraceptive. She had given birth four months earlier.

Ethinylestradiol with drospirenone has been approved as an oral contraceptive in all European Union countries since 2000 and has recently been launched in the United Kingdom.[2] The public assessment report of the contraceptive gives only one suspected case of pulmonary embolism but also says that the number of cases in the preregistration studies are too low for a reliable conclusion on this matter.[3]

The risk of thromboembolism for women using the third generation (combined) pill has long been debated. Physicians therefore may prefer a new type of combined pill, like ethinylestradiol with drospirenone, assuming that these are safer. However, an association of these drugs with a lower risk of thromboembolism has not been proved by research, and our cases show that newer contraceptive pills may have a risk of thromboembolism. At present, insufficient data on the superiority of ethinylestradiol with drospirenone are available.

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