Association of gestational diabetes mellitus with overall and type specific cardiovascular and cerebrovascular diseases


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Study question Is a history of gestational diabetes mellitus associated with an increased risk of overall and type specific cardiovascular and cerebrovascular diseases?

Methods In this systematic review and meta-analysis, PubMed, Embase, and the Cochrane Library were searched from inception to 1 November 2021 for observational studies that reported the association between gestational diabetes mellitus and incident cardiovascular and cerebrovascular diseases. The search was updated on 26 May 2022. Cardiovascular and cerebrovascular diseases was defined as the composite of cardiovascular diseases (including angina pectoris, myocardial infarction, coronary artery diseases, cardiovascular procedures, heart failure, and cardiovascular death) and cerebrovascular diseases (ischaemic stroke, haemorrhagic stroke, and transient ischaemic attack). Certainty of evidence in the included studies was appraised by the Grading of Recommendations, Assessment, Development, and Evaluations.

Study answer and limitations 15 studies rated as moderate or serious risk of bias were included. Of 513 324 women with gestational diabetes mellitus, 9507 had cardiovascular and cerebrovascular diseases. Of more than eight million control women without gestational diabetes, 78 895 had cardiovascular and cerebrovascular diseases. Compared with women without gestational diabetes mellitus, women with a history of gestational diabetes mellitus showed a 45% increased risk of overall cardiovascular and cerebrovascular diseases (risk ratio 1.45, 95% confidence interval 1.36 to 1.53), 72% for cardiovascular diseases (1.72, 1.40 to 2.11), and 40% for cerebrovascular diseases (1.40, 1.29 to 1.51). Women with gestational diabetes mellitus showed increased risks of incident coronary artery diseases (1.40, 1.18 to 1.65), myocardial infarction (1.74, 1.37 to 2.20), heart failure (1.62, 1.29 to 2.05), angina pectoris (2.27, 1.79 to 2.87), cardiovascular procedures (1.87, 1.34 to 2.62), stroke (1.45, 1.29 to 1.63), and ischaemic stroke (1.49, 1.29 to 1.71). The risk of venous thromboembolism was observed to increase by 28% in women with previous gestational diabetes mellitus (1.28, 1.13 to 1.46). Certainty of the evidence was judged as either low or very low quality. Limitations included the nature of observational studies, moderate or serious risk of bias in selected studies, potential confounding bias, and low or very low quality evidence.

What this study adds Gestational diabetes mellitus is associated with increased risks of overall and type specific cardiovascular and cerebrovascular diseases that cannot be solely attributed to conventional cardiovascular risk factors or subsequent diabetes.

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Marginal status and survival outcomes after breast cancer conservation surgery

Bundred JR, Michael S, Stuart B, et al
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Study question Does the width of margin clearance after breast conserving surgery for cancer affect subsequent distant and local recurrence?

Methods The associations between pathological margin status (distance of tumour from the inked margin) and distant and local recurrence were assessed in patients undergoing breast conserving surgery for early breast cancer. Where possible, each patient’s pathology was categorised as tumour at inked margin, close (no tumour at ink but <2 mm from margin), and negative (tumour >2 mm from margin).

Study answer and limitations 68 studies from 1 January 1980 to 31 December 2021, comprising 112 140 patients with breast cancer, were included. From 33 studies of 71 185 patients that reported on tumours within 2 mm of the inked margin, a pooled estimate prevalence of 17.8% (95% confidence interval 13.0% to 23.9%) of patients had tumour at ink or a close margin (<2 mm). The rate of distant recurrence was 25.4% (14.5% to 40.6%) in patients with tumour on ink, 8.4% (4.4% to 15.5%) in patients with tumour on ink or close, and 7.4% (3.9% to 13.6%) in patients with negative margins. Compared with negative margins, tumour on ink margins were associated with increased distant recurrence (hazard ratio 2.10 (95% confidence interval 1.65 to 2.69), P<0.001; I²=38%) and local recurrence (1.98 (1.66 to 2.36), P<0.001; I²=0%). Close margins were associated with increased distant recurrence (1.38 (1.13 to 1.69), P<0.001; I²=0%) and local recurrence (2.09 (1.39 to 3.13), P<0.001; I²=55%) compared with negative margins, after adjusting for receipt of adjuvant chemotherapy and radiotherapy.

What this study adds An association between tumour distance from the surgical margin after breast conserving surgery for cancer and distant recurrence exists. Close margins and tumour on ink is associated with increased distant and local recurrence, independent of chemotherapy and radiotherapy.

Funding, competing interests, and data sharing No specific funding received. NJB received a National Institute for Health and Care Research Research for Patient Benefit Grant investigating a margin device. Data are available on reasonable request.

Systematic review registration PROSPERO CRD42021232115.
Width of excision margin after breast conserving surgery for invasive breast cancer, and distant recurrence and survival

One premise of cancer treatment is that if a tumour is cut out but tumour cells remain present or close to the edges (of the cut), the risk of cancer returning at the same site is increased. Increased surgical focus on adequacy of margin excision would improve breast cancer survival worldwide.

Margin involvement is associated with poorer recurrence and survival outcomes in colorectal cancer. Most patients with early breast cancer are treated with breast conserving surgery. Removing cancers without leaving malignant cells at a surgical margin reduces local recurrence, but the effects of margin involvement on distant recurrence and mortality are unclear. How far the tumour should be from the specimen margin to ensure optimum oncological outcomes is contentious.

The definition of a clear margin matters

When a tumour is surgically removed, it is subject to pathological examination. The edges of the specimen, known as the margins, can be either microscopically involved (tumour at edge of specimen) or not involved (tumour not at edge). The distance from the edge of the margin to the tumour is measured. A close margin occurs when the tumour is within a given distance; usually 1 mm or 2 mm. Close margins are important because pathological assessment provides a representative sample of material examined. Involved or close margins are associated with 39% to 85% of patients having residual cancer after re-excision surgery. Occult foci of disease occur beyond the apparent edge of cancers and might not be adequately treated by adjuvant treatment.

Involved margins compared with negative margins were associated with increased distant recurrence

Internationally, surgical margin involvement in breast cancer varies from 9.4% to 17.8% depending on the definition of involvement. Differences in guidelines have led to confusion about the correct approach to surgical margins. Local recurrence is associated with higher rates of death from breast cancer. Globally, local recurrence rates after breast surgery have reduced from 20% before widespread use of adjuvant treatment to 5% or lower currently. The effect of both adjuvant systemic treatment and radiotherapy in reducing local and distant recurrence has probably influenced the interpretation of the significance of margin proximity.

To answer the questions of whether involved or close margins are associated with increased distant recurrence and decreased overall survival, we conducted a prospectively registered systematic review.

Patients’ pathology specimens were categorised as tumour at the margin (involved), close margins (tumour ≤2 mm from margin, but not at margin), and negative margins (tumour >2 mm from margin).

We included 68 studies with 112 140 patients undergoing breast conserving surgery. Overall, 9.4% (95% confidence interval 6.8% to 12.8%) of patients had tumours at the margin and 17.8% (13.0% to 23.9%) had tumours at or close to the margin. The rate of distant recurrence was 25.4% (14.5% to 40.6%) in patients with tumours at the margin, 8.4% (4.4% to 15.5%) with tumours at or close to margins, and 7.4% (3.9% to 13.6%) with negative margins.

On multivariable analyses, taking into account postoperative chemotherapy and radiotherapy, involved margins compared with negative margins were associated with increased distant recurrence (hazard ratio 2.10 (95% confidence interval 1.65 to 2.69) and local recurrence (1.98 (1.66 to 2.36)). Compared with negative margins, close margins were associated with increased distant recurrence (1.38 (1.13 to 1.69), P<0.001) and local recurrence (2.09 (1.39 to 3.13), P<0.001).

Limitations

Most of our data are from cohort studies; thus a causal association between margin proximity and outcomes cannot be proven. Given the absence of randomised evidence, these findings plausibly indicate that clearance of margins in invasive breast cancer should remain a priority to reduce both distant and local recurrence irrespective of the increased use of adjuvant treatments.

Why surgical tumour margins matter

Recognising that wider margins might require further surgery, decisions about re-excision should be the product of an informed discussion between clinicians and patients. The issue of involved margins after breast conservation may not be routinely discussed with patients, but patient advocates believed that complete surgical excision to prevent distant recurrence was more important to them than cosmesis. In multidisciplinary team meetings, opinions vary on what margin width is acceptable for invasive and in situ cancer. International guidelines on the optimal width for margin clearance should be based on the width to prevent distant recurrence as a primary aim. Wider margins should not necessarily increase mastectomy rates but might require more specific preoperative multidisciplinary team planning of surgical incisions and operations.

Conclusions

These comprehensive data indicate the likelihood that inadequate margin width results in higher risks of distant recurrence and breast cancer mortality, as well as increased local recurrence.

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FAST FACTS

Width of excision margin after breast conserving surgery for invasive breast cancer, and distant recurrence and survival

One premise of cancer treatment is that if a tumour is cut out but tumour cells remain present or close to the edges (of the cut), the risk of cancer returning at the same site is increased. Increased surgical focus on adequacy of margin excision would improve breast cancer survival worldwide.
Modifiable risk factors and long term risk of type 2 diabetes among individuals with a history of gestational diabetes mellitus

Yang J, Qian F, Chavarro JE, et al

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Study question Can having optimal levels of modifiable risk factors affect progression to type 2 diabetes in individuals with a history of gestational diabetes mellitus?

Methods This study included 4275 women with clinically diagnosed gestational diabetes mellitus and repeated measurements of weight and lifestyle factors followed up from 1991 to 2019. Five modifiable risk factors were assessed: not being overweight or obese (body mass index <25.0), high quality diet (top two groups of the modified Alternate Healthy Eating Index (divided by quintiles)), exercising regularly (≥150 min/week of moderate intensity or ≥75 min/week of vigorous intensity), moderate alcohol consumption (5.0-14.9 g/day), and no current smoking. Genetic susceptibility for type 2 diabetes was characterised by a genetic risk score based on 59 single nucleotide polymorphisms that were associated with type 2 diabetes in a subset of participants (n=1372). The number of optimal modifiable factors was aggregated and ranged from 0 to 5. The outcome assessed was incident type 2 diabetes.

Study answer and limitations Over a median 27.9 years of follow-up, 924 women developed type 2 diabetes. Compared with individuals who did not have optimal levels of any of the risk factors for the development of type 2 diabetes, those who had all five factors had 90% lower risk of the disorder. Hazard ratios for having optimal levels of one, two, three, four, and five factors compared with none was 0.94 (95% confidence interval 0.59 to 1.49), 0.61 (0.38 to 0.96), 0.32 (0.20 to 0.51), 0.15 (0.09 to 0.26), and 0.08 (0.03 to 0.23), respectively (P trend <0.001). The inverse association of the number of optimal levels of modifiable factors with type 2 diabetes was seen even in women who were overweight or obese or with higher genetic susceptibility (P trend <0.001). Limitations of this study included its observational nature as well as lack of information on the severity of gestational diabetes mellitus.

What this study adds Adherence to optimal levels of multiple modifiable risk factors was associated with a more than 90% lower risk of progression to type 2 diabetes in women with a history of gestational diabetes mellitus. The potential beneficial association was seen even among overweight or obese women and among women with greater genetic susceptibility to type 2 diabetes.

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