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How many cervical cancers are prevented by treatment of screen-detected disease in young women?

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Others have argued that as many as a third of women treated for high-grade cervical intraepithelial neoplasia (CIN) would have developed cervical cancer in the absence of screening and treatment. Under various assumptions and using past data on CIN grade 3 (CIN3) registrations in England and Scotland, we estimate what cervical cancer rates would have been in the absence of screening. Data on registrations of cervical carcinoma *in situ* for England and Scotland were used to project the additional numbers of invasive cervical cancers that would have resulted had the carcinoma *in situ* not been treated. We compare the resulting cervical cancer rates (under different models) with rates recorded in Cancer Incidence in 5 Continents. In order for the projected rates in England and Scotland at ages 20–24 not to be exceptionally high compared to maximum recorded rates for each registry in Cancer Incidence in 5 Continents, the progression rate from CIN3 to invasive cancer in women aged 20–24 should not exceed 1% per year. Similar progression rates were reasonable for women aged 25–29. Under the previously accepted assumption of 4.33% progression per year, cervical cancer rates in women aged 20–29 in both England and Scotland would have been 2–5 times greater than any observed rate (other than one registry, based on just 4 cases). From this analysis, at most 1.5% of women treated (equivalent to 3% of CIN3 registrations) would have had cancer by age 25, whereas it is reasonable to assume that over half of them would have regressed by age 25.
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Key words: cervical cancer; cervical intraepithelial neoplasia; screening; carcinoma *in situ*; cancer registration

Case–control studies of cervical screening in the UK indicate that screening has little impact on cervical cancer incidence in young women,[1,2] which was confirmed by a small Italian study[3]; however, a recently published Swedish study disagreed.[4] The finding that screening has little impact on cervical cancer incidence in young women is seemingly contradicted by the large numbers of women treated in their early 20s for high-grade cervical intraepithelial neoplasia (CIN).[5] Based on standard assumption about the natural history of CIN and the success of treatment, it is argued that through screening many (if not most) of those treated have been spared from cervical cancer.

Here we look at the internal consistency of this argument. Under various assumptions, and using past data on CIN grade 3 (CIN3) registrations in England and Scotland, we estimate what cervical cancer rates would have been in the absence of screening. These projections are compared to rates observed in different populations worldwide, over the last 50 years.

Material and methods

Using data on registrations of cervical carcinoma *in situ* (CIS) (CIN grade 3, ICD-9 code 233.1, ICD-10 code D06) for 1990–2005 in England and for 1989–2004 in Scotland, we project the additional numbers of invasive cervical cancers that would have resulted had the CIS not been treated. We then compared the resulting cervical cancer rates (under different models) with rates recorded in Cancer Incidence in 5 Continents (volumes I–IX).[6,7]

The number of registered cases of CIN3, by 5-year age groups, were obtained for England and Wales for 1990–1994[8] and for England for 1995–2005[9] from the Office for National Statistics (ONS: Series MB1). For 1990–1994, the numbers in England in each age-group were estimated by multiplying the numbers in England and Wales in that age-group by the proportion of the total number of CIN3 registrations (at all ages) that came from England. For 1999–2005, we compared the total numbers of registrations for CIN3 to the numbers of cases reported by colposcopy clinics and published in the annual Statistical Bulletins of the Cervical Screening Program.[5,10] In particular, we used the colposcopy data to estimate the numbers of cases of CIN grade 2 (CIN2) treated, in addition to the registered numbers of cases of CIN3. Annual registrations of CIN3 in Scotland for 1980–2004 were obtained from Information Services Division Scotland.[11]

Invasive cervical cancer rates in 5-year age groups were downloaded for both the original and the updated data for every entry in each volume of Cancer Incidence in 5 Continents which includes data from 1958 to 2002 (n = 1,302 rates per age group).[6,7] We used the updated rates where available and the originals where no updated data were provided; we also double checked that there was no overlapping years of data for each registry. We then estimated the number of women-years used in each rate and grouped rates according to whether they were based on more or less than 100,000 women-years. Where the women-years were less than 100,000 the rates were averaged with the rates in the next volume for the same age group and registry. If there were no relevant data in the subsequent volume the rate from the single volume was used. For each registry (and in each age group), we selected the highest rate over time (n = 442 rates per age group). The top 5 rates in each age group were checked in the Cancer Incidence in 5 Continents books to make sure there were no special circumstances under which the data were recorded. Details regarding data cleaning and selection can be found in the Appendix.

We assigned cases of CIN3 from 5-year age bands to single years of age using fixed proportions. The proportions were based on observed numbers of women in 1-year age-groups with CIS of the cervix (ICD-10 D06) diagnosed between 1990 and 2005, and resident in South East England (Kings Collage London, Thames Cancer Registry, unpublished data). Proportions used in this study are given in Table I.

Projections of cervical cancers in the absence of screening were made using a discrete-time exponential model for progression from CIN3 to invasive cancer. (For rate ρ with N women at risk at the beginning of the year, we assume that ρN will progress within 1 year). Following Parkin *et al.*[12] we used an annual rate of 4.33% corresponding to 36% progressing after 10 years and 50% after ~16 years. We also considered rates of 3, 2, 1, 0.5 and 0.2%, corresponding to 10-year progressions of 26, 18, 10, 5 and 2%, respectively. We also allowed for progression from CIN2 to CIN3. Our model for CIN2 assumed equal rates of progression and regression. (Equivalently, we used an exponential distribution with twice the rate, in which only half of the events were progres-

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TABLE I – PERCENTAGES OF WOMEN WITH CARCINOMA *IN SITU* OF THE CERVIX (ICD-10 D06) WITHIN EACH 5-YEAR AGE GROUP AND DIAGNOSED BETWEEN 1990 AND 2005 IN SOUTH EAST ENGLAND

Age	Percentage of age 15–19	Age	Percentage of age 20–24	Age	Percentage of age 25–29	Age	Percentage of age 30–34
15	1	20	10	25	19	30	23
16	3	21	15	26	20	31	22
17	12	22	19	27	20	32	20
18	28	23	26	28	21	33	18
19	56	24	30	29	20	34	16
15–19	*100*	*20–24*	*100*	*25–29*	*100*	*30–34*	*100*

TABLE II – PROJECTED RATES OF CERVICAL CANCER AT AGE 20–24

Progression rates from CIN3		Progression rates from CIN2			
		0	10%	25%	50%
0	England	2.4			
	Scotland	4.6			
0.20%	England	3.2	3.3	3.4	3.4
	Scotland	5.8	6.0	6.1	6.2
0.50%	England	4.4	4.6	4.8	5.0
	Scotland	7.6	8.0	8.3	8.6
1%	England	6.4	6.8	7.2	7.6
	Scotland	10.6	11.3	11.9	12.5
2%	England	10.2	11.1	11.9	12.7
	Scotland	16.5	17.8	19.1	20.2
3%	England	14.0	15.2	16.5	17.6
	Scotland	22.3	24.2	26.0	27.8
4.33%	England	18.9	20.7	22.4	24.1
	Scotland	29.7	32.4	35.1	37.5

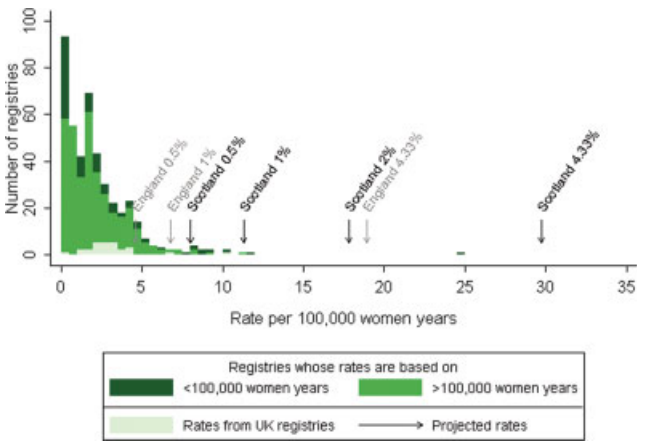

FIGURE 1 – Observed cervical cancer rates in women aged 20–24 with projected rates for England and Scotland under various scenarios marked. The projections based on 4.33% progression of CIN3 do not allow for progression from CIN2 to CIN3. The other projections all include 10% progression (and 10% regression) from CIN2 to CIN3 each year. Note: The rate for each registry is the highest rate from Cancer Incidence in Five Continents (generally based on 5 years of data), see Material and methods. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

sion to cancer.) We considered progression rates of 0 (*i.e.* no progression), 10, 25 and 50%. (Note that with 50% progression rate, half the cases of CIN2 become CIN3 after exactly 1 year and half never progress.) The rates corresponding to 0% progression from CIN3 are simply the observed cancer registration rates. Screening works by treating CIN which in the absence of screening would have progressed to cancer. Under the assumption of no progression, cancer rates would not have been affected by screening.

Results

Nationally reported colposcopy data from England indicate that the number of cases of CIN2 is ~70% of the number of cases of CIN3. They also show that (even ignoring the incomplete reporting of histology from a few colposcopy clinics) the numbers of cases of CIN3 registered with the cancer registries are only about 80% of the total reported by colposcopy. Thus for simplicity we use the number of registered cases of CIN3 and assume an equal number of cases of CIN2. (In reality, some of the cases of CIN2 would have been CIN3.)

The rates of cervical cancer that would have been observed in women aged 20–24 in England in 2005 and in Scotland in 2004 are presented in Table II (because of the smaller numbers in Scotland, we use a base of the average rate for 1999–2004). At 4.33% progression per year, the rate of prevented cervical cancer in women aged 20–24 would have been 16.5 per 10,000 in England and 25.1 per 100,000 in Scotland (corresponding to total rates of 18.9 and 29.7 per 100,000 women years, respectively), even assuming that there is no progression from CIN2. Allowing for some progression from CIN2 to CIN3, one would be projecting an underlying rate per 100,000 of over 20 in England and over 30 in Scotland (Table II).

Data from Cancer Incidence in 5 Continents show that the only registry with rates exceeding 12 per 100,000 in women aged 20–24 is Yukon, Canada, in 1983–1997, with a rate of 24.8/100,000 (Fig. 1). This rate was based on 4 cases; the lower 95% confidence interval for the rate is 6.76. The second highest rate is for Alameda County, CA, in 1960–1973, among black women, which is 11.9/100,000 (based on 7 cases). Only 13 (3.2% of) registries have ever recorded a rate greater than 8 per 100,000, in this age group. Figure 1 shows where a number of the projections from Table II would fall on a histogram of maximum rate per registry from Cancer Incidence in 5 Continents.

For the projected rates in Scotland at ages 20–24 not to be more than 9 per 100,000 (only 7 registries observed rates greater than that), the progression rate from CIN3 to invasive cancer in women aged 15–24 should be between 0.5 and 1% per year. Assuming 1% progression from CIN3 to cancer and zero progression from CIN2 to CIN3, we project a rate per 100,000 of 6.4 in England and 10.6 in Scotland (Table II). Only 3 (0.7%) of the observed rates were above 10.6.

The rates of cervical cancer that would have been observed in women aged 25–29 and 30–34 are presented in Tables III and IV, respectively. As with the younger age-group, the projected rates for Scotland are considerably higher than for England, reflecting higher rates of CIN3 in Scotland. Progression rates of between 0.5 and 1% per year would lead to cervical cancer rates in women aged 25–29, which are about as big as any recorded by Cancer Incidence in 5 Continents. [There are 5 registries with rates of over 30 and none greater than 35 (Fig. 2).] Progression from CIN3 of 0.5% per year would yield cancer rates of between 27 and 33 per 100,000 in Scotland. Progression rates of 1% per year from CIN3 would yield cancer rates of between 29 and 37 per 100,000 in England (Table III). At a progression rate of 2% per year (even without allowing for progression from CIN2), the projected rates at age 25–29 for both England and Scotland would be greater than any recorded by Cancer Incidence in 5 Continents. Under the model used by Parkin *et al.*[12] (4.33% progression annually) the rates in women aged 25–29 would have been 2 to 3 (2.3–3.5) times greater than any recorded rates (even without allowing for progression from CIN2) (Table III).

TABLE III – PROJECTED RATES OF CERVICAL CANCER AT AGE 25–29

Progression rates from CIN3		Progression rates from CIN2			
		0	10%	25%	50%
0	England	12.1			
	Scotland	13.4			
0.20%	England	15.7	16.4	16.9	17.1
	Scotland	19.1	20.2	21.0	21.4
0.50%	England	20.9	22.7	23.9	24.6
	Scotland	27.4	30.3	32.2	33.3
1%	England	29.5	33.0	35.4	36.8
	Scotland	41.0	46.8	50.4	52.6
2%	England	46.0	52.9	57.5	60.2
	Scotland	67.0	78.3	85.4	89.6
3%	England	61.6	71.7	78.4	82.4
	Scotland	91.5	108.1	118.5	124.5
4.33%	England	81.0	95.2	104.6	110.1
	Scotland	122.0	145.2	159.8	168.0

TABLE IV – PROJECTED RATES OF CERVICAL CANCER AT AGE 30–34

Progression rates from CIN3		Progression rates from CIN2			
		0	10%	25%	50%
0	England	16.7			
	Scotland	18.5			
0.20%	England	22.5	24.2	24.9	25.2
	Scotland	27.1	29.7	30.7	31.1
0.50%	England	31.1	35.2	16.7	37.7
	Scotland	39.7	46.1	48.6	49.6
1%	England	44.7	52.9	56.3	57.6
	Scotland	59.9	72.4	77.2	79.1
2%	England	70.1	85.9	92.4	94.9
	Scotland	97.1	121.2	130.4	133.8
3%	England	93.1	116.0	125.2	128.7
	Scotland	130.5	165.5	178.5	183.2
4.33%	England	120.3	151.9	164.4	168.9
	Scotland	169.8	217.9	235.4	241.5

The results for women aged 30–34 are similar (Table IV and Fig. 3). Assuming a progression rate of 4.33% annually, the rates in Scotland would have been 3–4 times higher than any observed previously. The highest observed rate (59.3/100,000) in this age group is for Bermuda: black in 1983–1987 and is based on 4 cases. (The next highest is 53.4/100,000.) At 1% per year (without progression of CIN2) the rates in Scotland would (in the absence of treatment of CIN3) have been similar to the highest ever observed. For England with 1% progression from CIN3 annually, one could allow 50% of CIN2 to progress to CIN3 in order to reach invasive cervical cancer rates of close to 58 per 100,000 women-years.

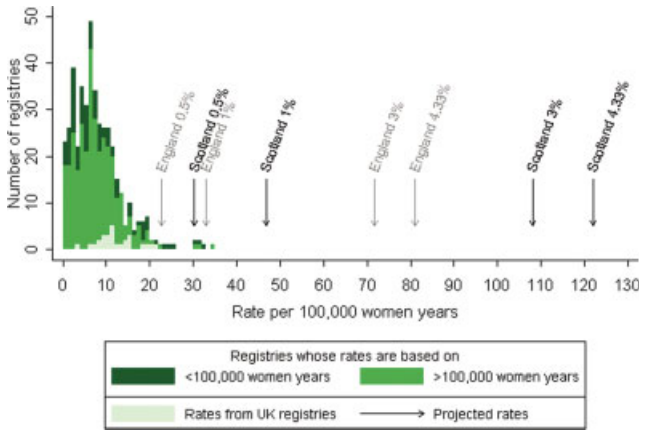

FIGURE 2 – Observed cervical cancer rates in women aged 25–29 with projected rates for England and Scotland under various scenarios marked. The projections based on 4.33% progression of CIN3 do not allow for progression from CIN2 to CIN3. The other projections all include 10% progression (and 10% regression) from CIN2 to CIN3 each year. The rate for each registry is the highest rate from Cancer Incidence in Five Continents (generally based on 5 years of data), see Material and methods. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

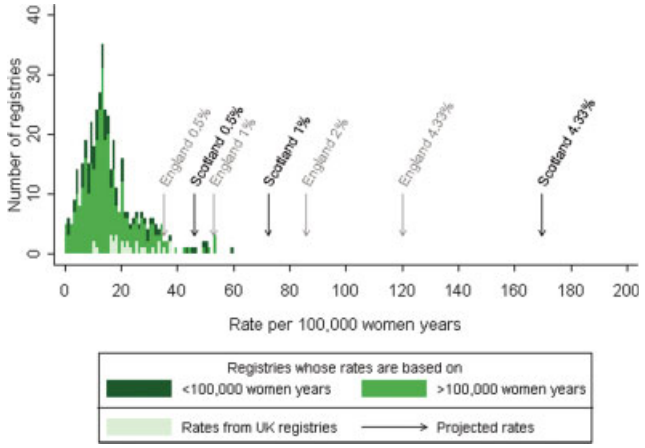

FIGURE 3 – Observed cervical cancer rates in women aged 30–34 with projected rates for England and Scotland under various scenarios marked. The projections based on 4.33% progression of CIN3 do not allow for progression from CIN2 to CIN3. The other projections all include 10% progression (and 10% regression) from CIN2 to CIN3 each year. The rate for each registry is the highest rate from Cancer Incidence in Five Continents (generally based on 5 years of data), see Material and methods. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Discussion

It is often said that the thousands of cases of CIN3 registered in young women are proof that cervical screening in young women is doing enormous good.[13] The basis for such a conclusion is the assumption that a substantial proportion (30–50%) of CIN3 would, if untreated, progress to invasive cervical cancer within 10–15 years as was seen in the New Zealand cohort reported by McIndoe *et al.*[14] and McCredie *et al.*[15] For instance, based on a comparison of screened and never-screened cohorts, Boyes *et al.*[16] estimated that between 26 and 53% of CIS would progress to cancer.

One needs to ask why progression rates in these early studies are seemingly so much greater than is consistent with the recent data from England and Scotland. One possible explanation is that disease diagnosed 30 years ago was more likely to progress than the disease detected more recently. This could be related to improvements in screening leading to smaller CIN3 lesions being detected. Tidbury *et al.*[17] showed that microinvasion was more likely to be seen in large CIN3 lesions than small ones, and Jarmulowicz *et al.*[18] showed that women with large CIN3 lesions were more likely to have moderate or severe dyskaryosis on cytology than were women with small CIN3 lesions.

Another possible explanation is that CIN3 in young women is less likely to progress than is CIN3 in older women. This could simply be a reflection of persistence—if most CIN3 starts in young women, lesions that have not regressed by age 30–40 may be more likely to progress. It has been suggested for some time that CIN3 (and even CIS of the cervix) does regress and that the rate of progression must be less in young women than in older women. Parkin[19] concludes that the progression rate of CIS is lower in young women (about 0.5% per year at age 20–24) than in

older women (increasing to 10% per year by age 80). Similar conclusions were reached by Prorock.[20] Furthermore, Morrisson *et al*.[21] estimated that 72% of CIS in a cohort of women aged 15–39 regressed compared to 47% in women aged 40–64.

A crucial question is what would have happened to women with CIN3 detected and treated aged 20–24 had they not been screened until 25. The main reason to screen under the age of 25 is the belief that many women treated for CIN2 and CIN3 under the age of 25 would have had invasive cancer had they not been screened until age 25. The main reason not to screen until 25 is the belief that screening younger women prevents few, if any, additional cancers, but leads to many thousands of women being treated for CIN2 and CIN3 that would have regressed by age 25. From this analysis, it would seem that at most 1.5% of women treated (equivalent to 3% of CIN3 registrations) would have had cancer by age 25. This analysis is in fact consistent with minimal benefit from treating CIN3 in women aged 20–24. Indeed analysis of trends in CIS and cervical cancer in Sweden do not support more than a very slow progression rate.[22] Although the number of cases of cervical cancer have fallen (by 43% in women aged 20–29 and by 27% in women aged 30–34) between 1968–1979 and 1992–2002, as a percentage of those treated for CIS aged 20–29 in 1980–1991 the fall (in both age groups combined) is just 3%. This corresponds to a progression of 0.3% per year. This should be balanced against the likelihood that over half of the CIN2 and CIN3 treated at ages 20–24 would have regressed (without treatment) by age 25.

These data alone are not enough to determine the effectiveness of cervical screening in young women; nevertheless, it should be clear that it is unreasonable to assume that, within 10 years, a third or even 10% of the CIN3 treated in the United Kingdom in woman aged 20–24 would have otherwise have progressed to invasive cancer. In our view, those who wish to screen women under age 25 need to provide evidence that its benefits outweigh its costs both to society and to individual women.

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APPENDIX – DATA CLEANING AND SELECTION

Original and updated data were checked to ensure that registries were not duplicated because of changes in the registries names, for example, "Japan, Miyagi" and "Japan, Miyagi Prefecture." It was noted that 2 Chinese registries did not provide cervical cancer data and were dropped (China, Changle and China, Cixian). We dropped the rates for "Northwest Territories and Yukon, Canada," as both these registries provided data separately. The same was the case for USA SEER data, which is a summary rate of all individual registries in the USA.

The top 5 rates in each age group were checked in the Cancer Incidence in 5 Continents books to make sure there were no special circumstances under which the data were recorded.

As a result the following rates were found to have included CIS and therefore were removed from the figures in this study:

1. Age 20–24: the fourth highest rate 11.09 (Canada, New Brunswick, 1962–1966).
2. Age 25–29: the two highest rates 38.54 (New Brunswick, Canada, 1962–1966) and 36.17 (El Paso County, TX, 1968–1970, in Hispanic women), together with the fifth highest rate 32.8 (Poland, Warsaw City, 1965–1966).
3. Age 30–34: four of five highest rates were dropped. They are 79.1 [Brazil, Pernambuco (Recife), 1980], 75.76 (New Brunswick, Canada, 1962–1966), 70.49 (El Paso, Texas: Hispanic, 1960–70) and 55.6 (Poland, Warsaw City, 1965–1966).

It is possible that some of the rates shown in the figures in this study include CIS.